I

GLYOXAL MONOACETAL AND A GENERAL SYNTHESIS OF α,β-UNSATURATED ALDEHYDES

II

AN APPROACH TO 13-METHYLPHENALENE-A BRIDGED [12]ANNULENE

by

PAUL DAVID NOIRE

A dissertation submitted to the Graduate Faculty in Chemistry in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York

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date

Executive Officer

Supervisory Committee

The City University of New York

Abstract

I

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II

AN APPROACH TO 13-METHYLPHENALENE-A BRIDGED [12]ANNULENE

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Paul David Noire

Adviser: Professor Klaus G. Grohmann

I

The heretofore inaccessible glyoxal monodiethylacetal has been synthesized in exceptionally high yield and purity by the low temperature ozonolysis of acrolein diethylacetal, (eq a).

$$H_2C{=}CH{-}CH(OEt)_2 \xrightarrow[2.\ CH_3SCH_3/0°C]{1.\ O_3/CH_3OH/-78°C} (EtO)_2CH{-}CHO \qquad \text{(eq a)}$$

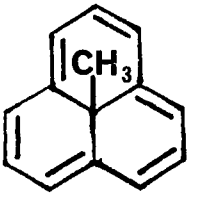
A general synthesis of α,β-unsaturated aldehydes has been developed by the Wittig condensation of glyoxal monoacetal and i. allylic and benzylic phosphoranes, ii. primary and secondary phosphoranes, and iii. stabilized phosphoranes, (eq b).

$$(C_6H_5)_3P{=}CRR' \quad + \quad (EtO)_2CH\text{-}CHO \longrightarrow RR'C{=}CH\text{-}CHO \qquad \text{(eq b)}$$

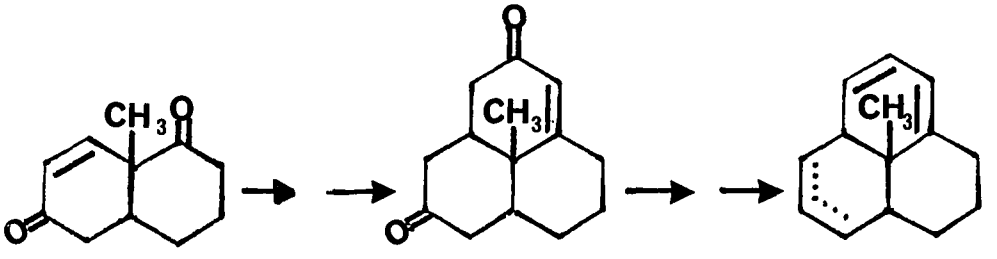
A precursor to the cyclohexyl components of the pheromone of the boll weevil has been synthesized using this approach.

II

A precursor to the long sought bridged [12]annulene, 13-methylphenalene, has been synthesized starting from cis-Δ^1-3,8-octalindione, (eq c). The key intermediate enedione, (eq c), was synthesized from cis-octalindione by a Michael reaction followed by ester cleavage and aldol condensation to afford a phenalene-type skeleton, (eq c). The enedione was then converted to the desired triene precursor by reduction and dehydration, (eq c).



13-Methylphenalene



(eq c)

Acknowledgement

The author wishes to express his gratitude to Professor Klaus G. Grohmann for his guidance, encouragement, and friendship during the course of this investigation. Mr. Mukund Sibi kindly obtained the ^{13}C-NMR spectra. Finally, the author wishes to express his appreciation to all his colleagues in the laboratory for their general help and advice.

Foreword

'The synthetic chemist is more than a logician and strategist; he is an explorer strongly influenced to speculate, to imagine, and even to create. These added elements provide the touch of artistry which can hardly be included in a cataloguing of the basic principles of Synthesis, but they are very real and extremely important. Further, it must be emphasized that intellectual processes such as the recognition and use of synthons require considerable ability and knowledge; here, too, genius and originality find ample opportunity for expression.

The proposition can be advanced that many of the most distinguished synthetic studies have entailed a balance between two different research philosophies, one embodying the ideal of a deductive analysis based on known methodology and current theory, and the other emphasizing innovation and even speculation. The appeal of a problem in synthesis and its attractiveness can be expected to reach a level out of all proportion to practical considerations whenever it presents a clear challenge to the creativity, originality and imagination of the expert in synthesis'.

E. J. Corey in Pure Appl. Chem., 14, 30 (1967).

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I

GLYOXAL MONOACETAL AND A GENERAL SYNTHESIS OF α,β-UNSATURATED ALDEHYDES

Chapter One

Previous Synthetic Approaches To α,β-Unsaturated Aldehydes

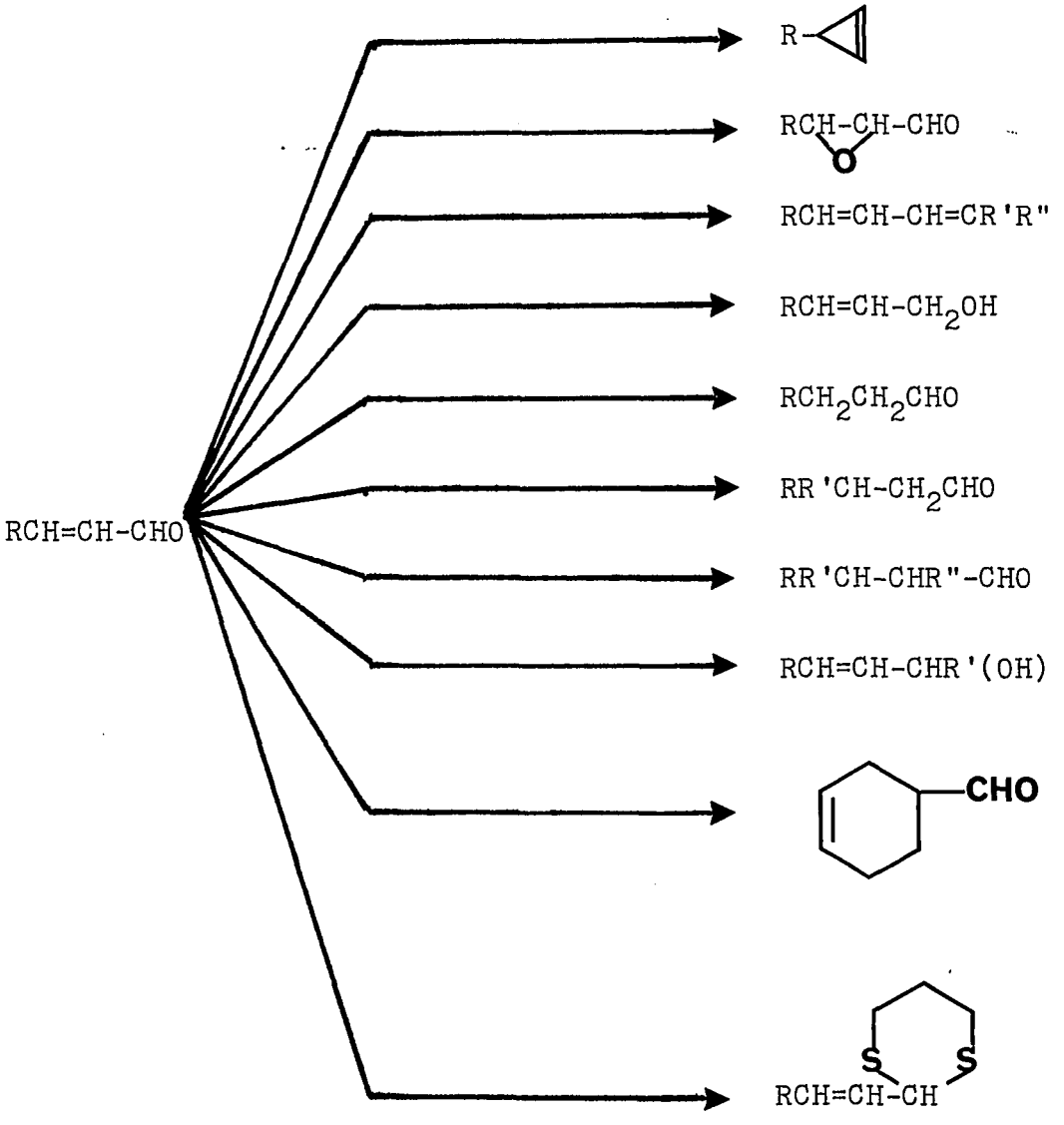
Synthetic organic chemists have often been compared with artists and architects. In fact a popular text is entitled "Art In Organic Syntheses".[1] One need only look at any of the excellent texts on natural products chemistry[2] to see how diverse and complex these molecules can be. There are many molecules of theoretical interest which also can challenge the skill of the synthetic organic chemist. Cubane and the still unknown dodecahedrane are just two examples.

Organic chemists are constantly engaged in the study of improving previous synthetic methodology. One example of this is in the steroid field. W. S. Johnson's biomimetic polyene cyclization has the potential of building the tetracyclic steroid nucleus from essentially acyclic precursors in <u>one</u> step, and with correct stereochemical orientation![3]

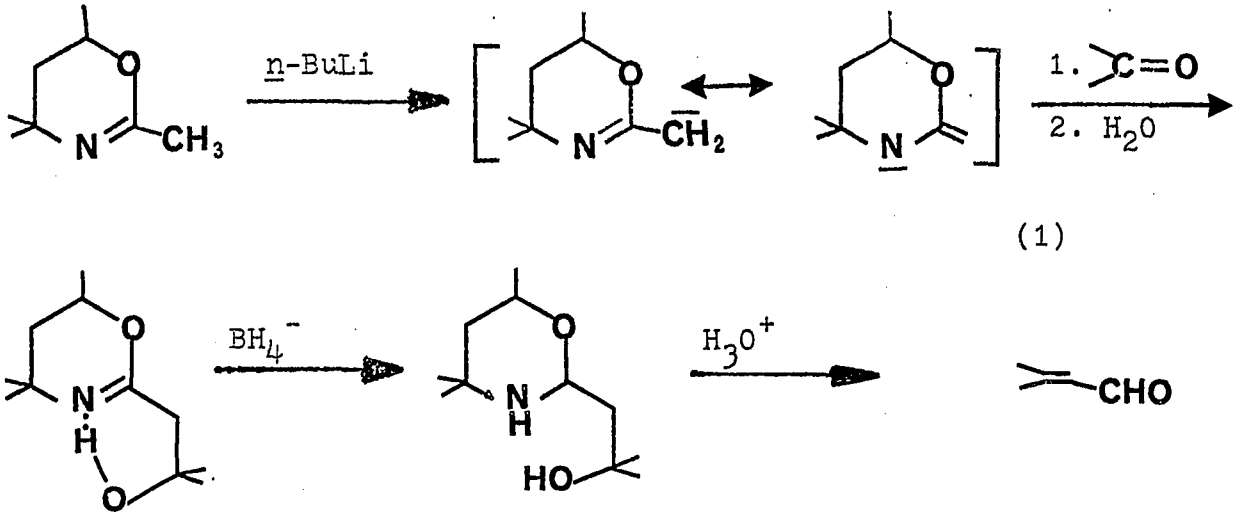
The α,β-unsaturated aldehyde unit is found in nature and has broad uses in transformations to other structural types. Some of these transformations are illustrated in summary form in Figure 1.

In view of their synthetic utility as intermediates and also as target molecules in natural products synthesis, the formation of the α,β-unsaturated aldehyde moiety has received some attention in the recent chemical literature. Some of these methods will be discussed and illustrated.

Figure 1. Some Transformations Of The Enal Moiety.



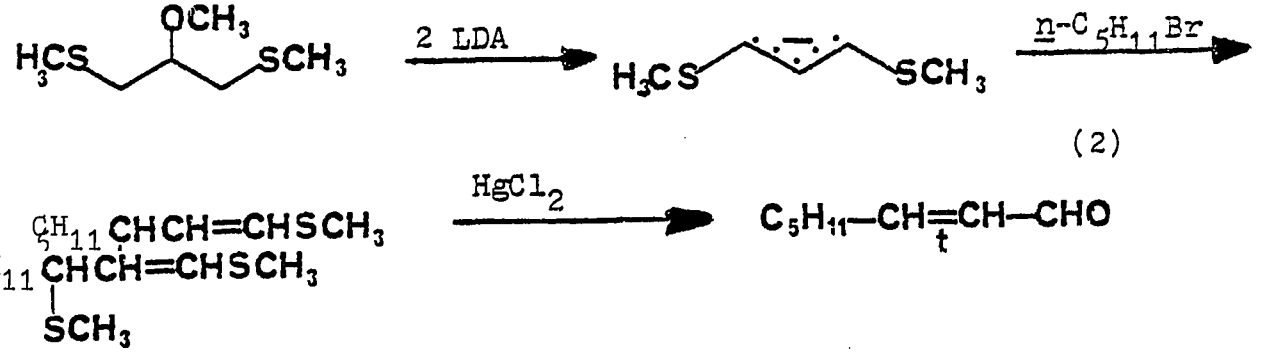
A. Meyers and co-workers have championed the use of 1,3-dihyrooxazines and their derivatives in a synthesis of α,β-unsaturated aldehydes and other types of aldehydes and ketones (eq 1).[4]



(1)

The yields in this sequence range from 40-60%. Note that in order to produce a carbonyl compound it is necessary to use a carbonyl compound as one of the reactants. One advantage of this approach is that sodium borodeuteride can be used in the reduction step. This results in deuterium incorporation at C-1 of the enal.

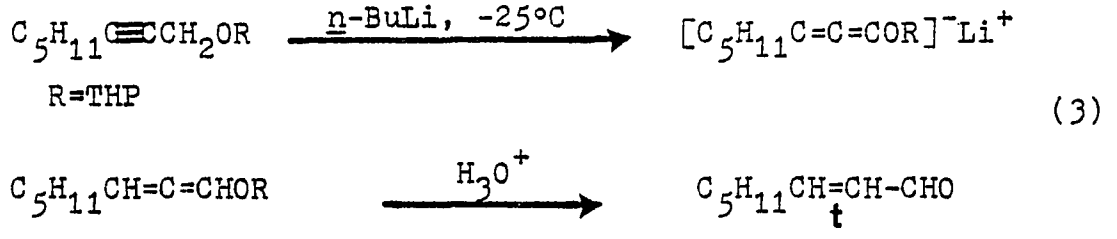
E. J. Corey and co-workers have used 1,3-bis(methylthio) allyllithium in a synthesis of enals.[5] This transformation is illustrated in eq 2.



(2)

The starting materials are easy to prepare and the yields are 70-80%. Another advantage is that an alkyl halide can be used to trap the allyllithium reagent. Alkyl halides are generally readily accessible.

In another synthesis of trans-2-octenal Corey and Terashima have used the commercially available 2-octyn-1-ol as shown in eq 3.[6]



(3)

In principle any propargylic alcohol can be used.

Leroux and Roman have used allenic and propargylic ethers to generate α,β-unsaturated aldehydes.[7] The reaction sequence is shown in eq 4.

$$C_5H_{11}\text{-}C{\equiv}C\text{-}CH_2OCH_3 \xrightarrow{\text{n-Butyllithium, -78°C}} C_5H_{11}\overline{C}{=}C{=}CHOCH_3 \quad (4)$$

$$\rightleftharpoons C_5H_{11}C{\equiv}C\text{-}\overline{C}HOCH_3 \xrightarrow{RX} C_5H_{11}CR{=}C{=}CHOCH_3$$

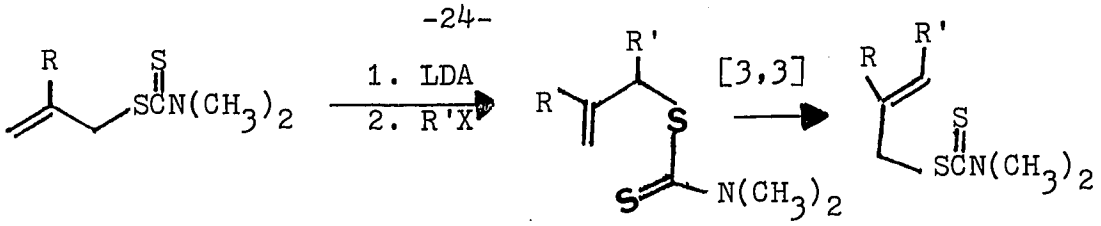
$R=CH_3$ (from $(CH_3)_2SO_4$)
$R=C_2H_5$ (from $(C_2H_5)_2SO_4$)
$R=Si(CH_3)_3$ (from $(CH_3)_3SiCl$)

$$\xrightarrow{H_3O^+} C_5H_{11}CR{=}CH\text{-}CHO$$

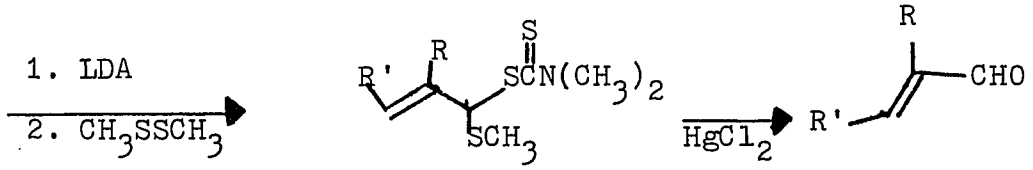
In a novel synthesis of enals Nakai and co-workers have used S-α-lithioallyl dithiocarbamates as the key intermediates and a [3,3]-sigmatropic rearrangement as the key step, (eq 5).[8]

Corey and co-workers have reported another synthesis of enals from primary tert-butyl imines, or N,N-dimethyl hydrazones by silylation, metalation, treatment with an aldehyde or ketone, and then hydrolysis to the enal. This work is shown in eq 6.[9a]

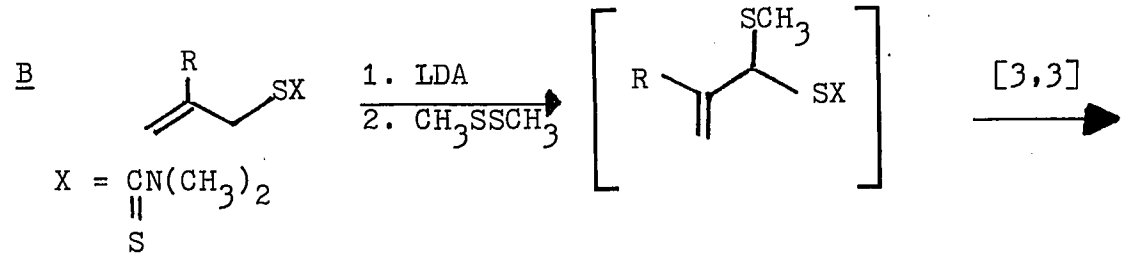
A

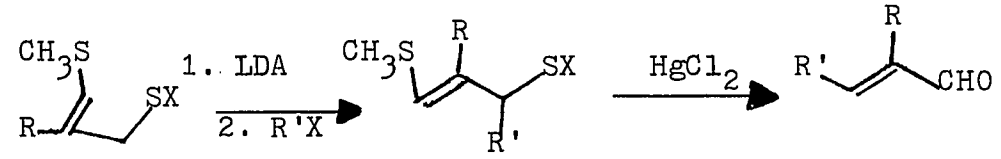

R
S
SCN(CH3)2
1. LDA
2. R'X
R'
R
S
S
N(CH3)2
[3,3]
R'
R
S
SCN(CH3)2

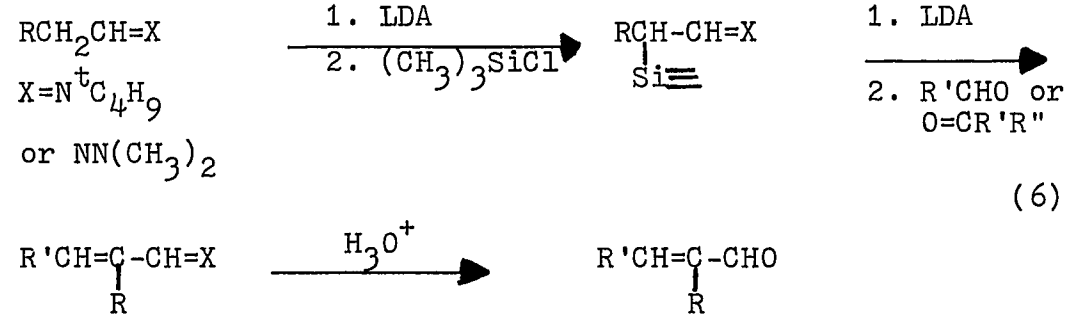
(5)


1. LDA
2. CH3SSCH3
R'
R
S
SCN(CH3)2
SCH3
HgCl2
R
R'
CHO

B

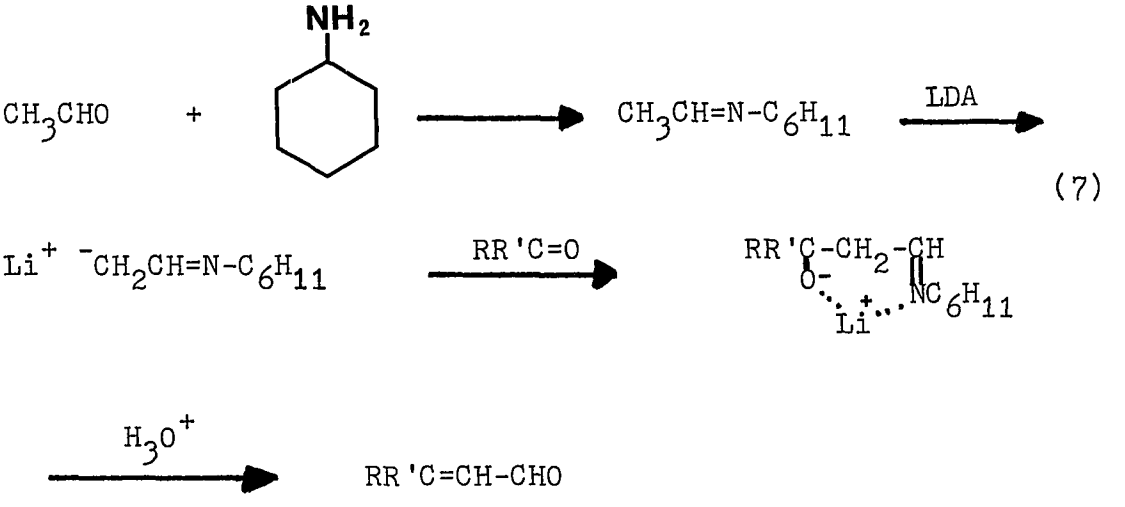

R
SX
X = CN(CH3)2
S
1. LDA
2. CH3SSCH3
SCH3
R
SX
[3,3]


CH3S
SX
R
1. LDA
2. R'X
CH3S
R
SX
R'
HgCl2
R
R'
CHO


RCH2CH=X
X=N tC4H9
or NN(CH3)2
1. LDA
2. (CH3)3SiCl
RCH-CH=X
Si
1. LDA
2. R'CHO or
O=CR'R"
R'CH=C-CH=X
R
H3O+
R'CH=C-CHO
R

(6)

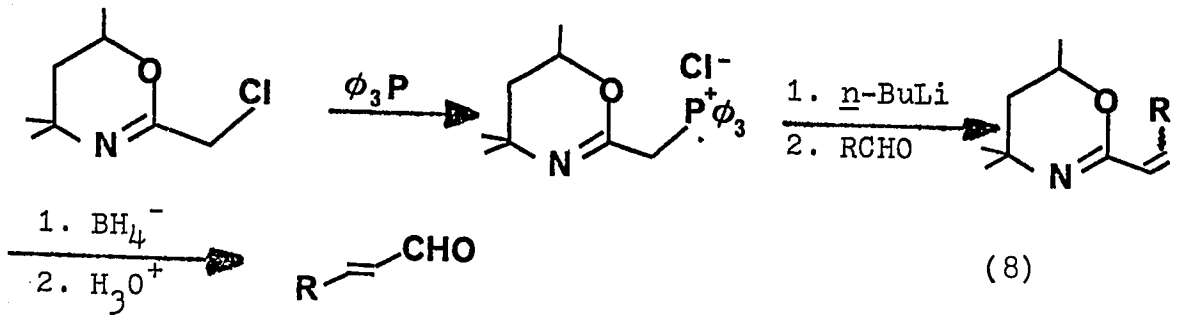
This particular work by Corey et al. is based on an extension of the pioneering work of Wittig and co-workers, who developed the principles of the directed aldol condensation through the intermediacy of metalated Schiff bases.[9b] This is illustrated in eq 7.



(7)

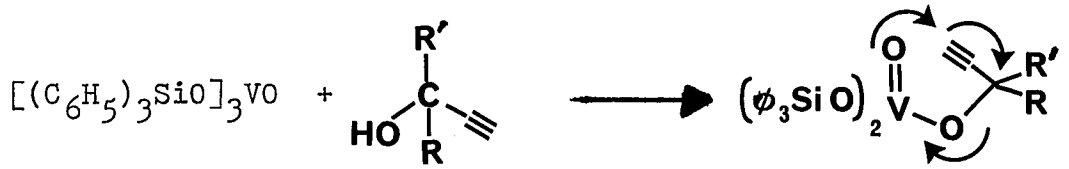
The metalated Schiff base can react with ketones and aldehydes. When the proton to be removed by lithium diisopropylamide (LDA) is made more sterically congested, the yields are found to decrease.

Meyers and Malone have reported an interesting modification of their earlier 1,3-oxazine work utilizing the phosphonium salt or phosphonate derived from 2-chloromethyl-1,3-oxazine.[10] This synthesis of α,β-unsaturated aldehydes and ketones is illustrated in eq 8.



(8)

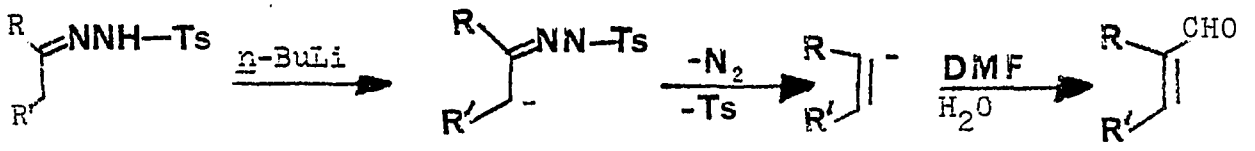
Pauling and co-workers have used the Meyer-Schuster rearrangement utilizing the new catalyst tris(triphenylsilyl)vanadate(V) in a synthesis of enals, (eq 9).[11]



(9)

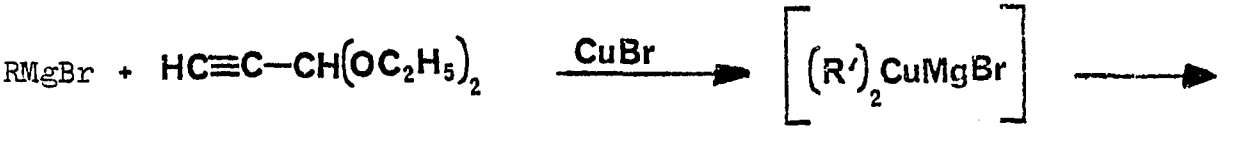
X=$[(C_6H_5)_3SiO]_2$

Traas has reported an efficient synthesis of α,β-unsaturated aldehydes from tosylhydrazones by trapping the intermediate lithium alkenyl with dimethylformamide (DMF) and subsequent hydrolysis, (eq 10).[12]

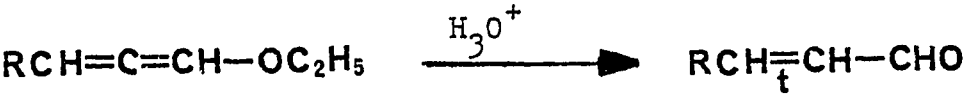


(10)

Using a copper(I) bromide catalyzed Grignard addition to propargyl aldehyde diethylacetal, Vermeer and co-workers have synthesized allenic ethers and enals. Their method is illustrated in eq 11.[13]

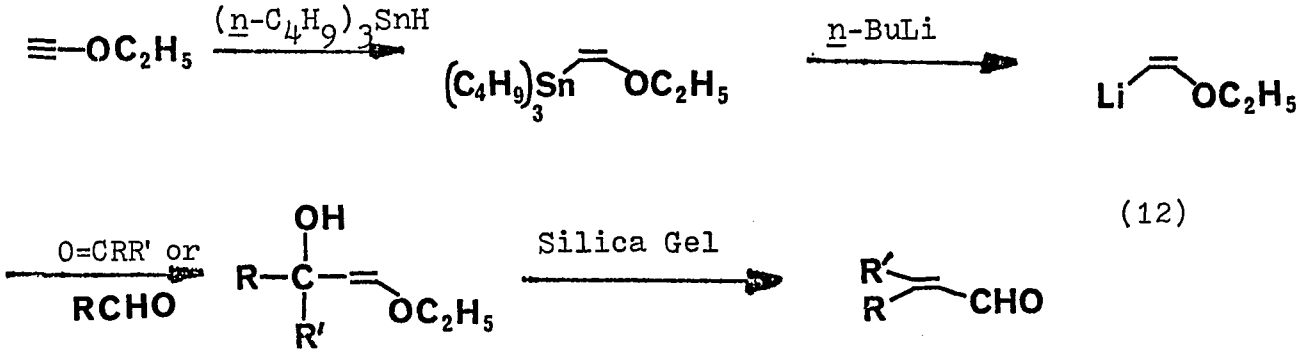


(11)



Wollenberg and co-workers have recently reported an efficient and fairly simple synthesis of α,β-unsaturated aldehydes.[14] They use a nucleophilic acetaldehyde equivalent,

namely cis-2-ethoxyvinyllithium. This compound is prepared from the hydrostannation of the commercially available ethoxyacetylene by treatment with n-butyllithium. The resulting vinyllithium compound is then trapped with an aldehyde or ketone. The reaction sequence is illustrated in eq 12.



(12)

Finally, a series of two carbon phosphoranes and phosphonates have been used in formylolefination reactions. Trippett and Walker prepared formylmethylenetriphenylphosphorane I, a stabilized phosphorane which reacts with aldehydes, but significantly not with ketones, to produce (E)-α,β-unsaturated aldehydes.[15a] This Wittig reaction is illustrated in eq 13.

$$\underset{\text{I}}{(C_6H_5)_3P{=}CH\text{-}CHO} + RCHO \longrightarrow RCH{=}CH\text{-}CHO \quad \text{(E isomer only)} \qquad (13)$$

Diethyl formylmethylphosphonate diethylacetal II has been prepared and its reaction with benzaldehyde has been studied.[15b] This phosphonate was found not to react with ketones.[15b,c] The reaction of II with benzaldehyde is shown in eq 14.

$$(C_2H_5O)_2P(O)CH_2CH(OC_2H_5)_2 \quad (II) \quad + \quad C_6H_5CHO \xrightarrow{NaNH_2} C_6H_5CH{=}CH{-}CH(OEt)_2 \quad (E \text{ isomer}) \qquad (14)$$

In an extension of the previous work (eq 14), Nagata and co-workers have used the cyclohexyl enamino phosphonate III in an efficient synthesis of enals. The phosphonates react with aldehydes and ketones, (eq 15).[15d]

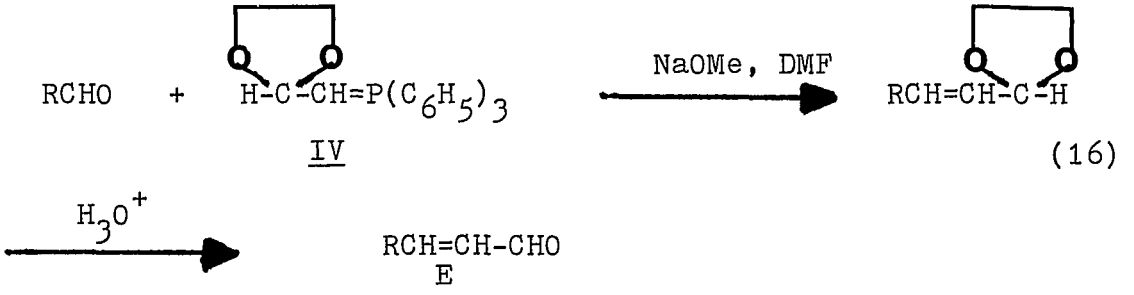
$$(EtO)_2P(O)\text{-}CR{=}CH\text{-}NH\text{-}C_6H_{11} \quad (III) \quad + \quad R'R''C{=}O \xrightarrow{NaH}$$

$$R'R''C{=}CR\text{-}CH{=}NC_6H_{11} \xrightarrow{H_3O^+} R'R''C{=}CR\text{-}CHO \qquad (15)$$

$$R{=}H,\ CH_3,\ \text{or}\ C_6H_5CH_2$$

Another useful formylolefination reagent is 1,3-dioxan-2-ylmethyltriphenylphosphonium bromide IV.[15e] This compound smoothly forms an ylid which then can react with aldehydes and enals to give the chain extended α,β-unsaturated aldehyde (E isomer only). The ylid also reacts with 9-fluorenone, but

much more sluggishly and in lower yield to afford after hydrolysis fluoren-9-ylideneacetaldehyde. The use of this dioxolan is illustrated in eq 16.

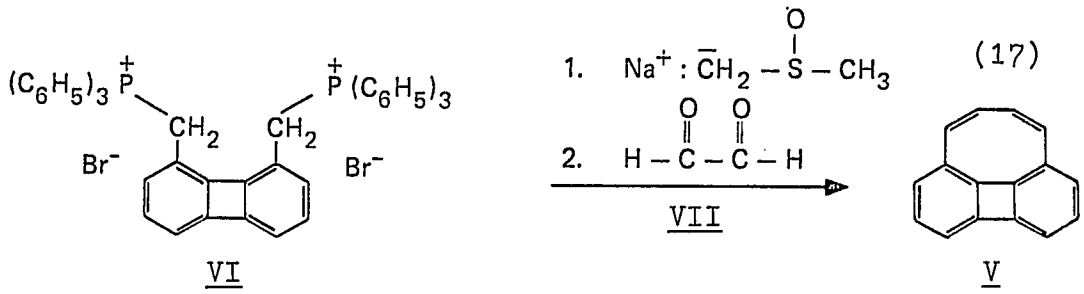


Some of the methods discussed are simple and give good yields of the α,β-unsaturated aldehydes. Others start with non-readily available compounds and go through a number of steps before the final product is obtained. In many of the above cases a common feature is the use of a ketone or aldehyde to produce the desired α,β-unsaturated aldehyde. The problem is that aldehydes and ketones may not always be readily available as a starting compound. If a general aldehyde or ketone component could be found, than the scope of formyl-olefination could be expanded considerably and made much more useful. The production of just such a general aldehyde component and its use in formylolefination (enalation) make up the remainder of the discussion.

Chapter Two

Discussion

Wilcox, Grohmann et al. have reported the synthesis of the unusual hydrocarbon V by reaction of the bis-phosphonium salt VI with dimsyl sodium and then with monomeric glyoxal VII.[16] (eq 17).



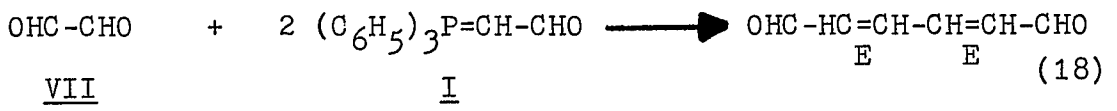
VI V

Besides the desired hydrocarbon V in 12% yield, large and variable amounts of the "undesired" α,β-unsaturated aldehydes were produced. Glyoxal was generated by the pyrolysis of the commercially available "glyoxal trimer" (MC&B). Monomeric glyoxal VII seemed the perfect synthon for the synthesis of enals and this goal was pursued in the first project

A. Synthesis of α,β-Unsaturated Aldehydes From Monomeric Glyoxal VII.

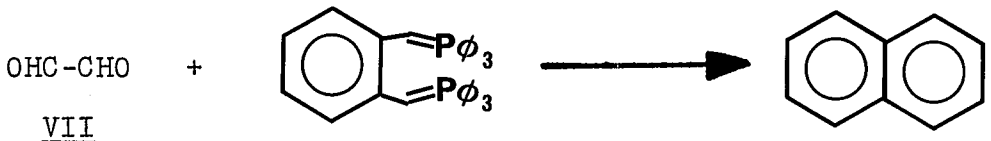
There are a number of reports in the literature concerning the Wittig reaction of glyoxal VII, or glyoxal precursors, such as the sodium bisulfate addition complex, with various Wittig reagents. These include the synthesis of muconaldehyde

by reaction of glyoxal VII with formylmethylenetriphenylphosphorane I, (eq 18),[17] the synthesis of 1,4-dipyridyl-1,3-butadiene, (eq 19),[18] and the synthesis of naphthalene by reaction of glyoxal VII with ortho-xylylene bis-phosphorane VIII, (eq 20).[19]



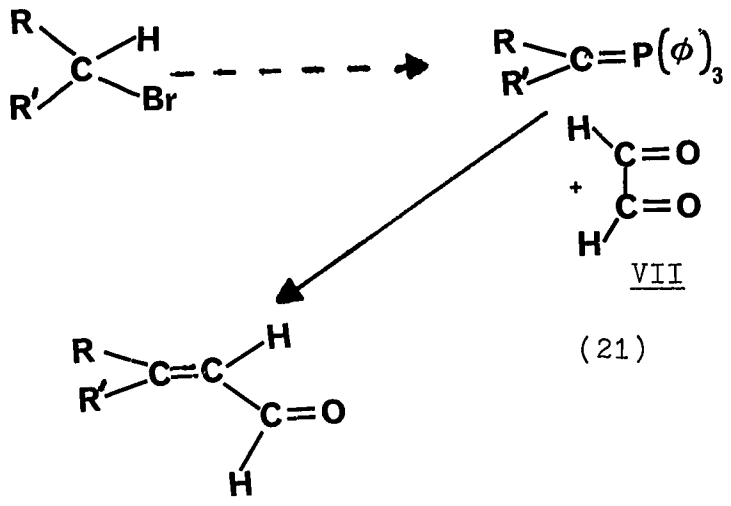
VII I (18)

VII (19)



VII VIII (20)

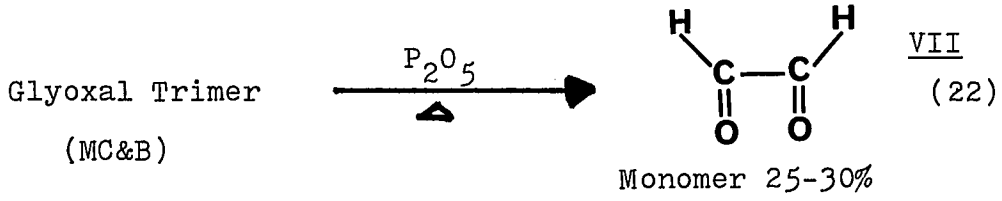
With these earlier references in hand it seemed logical to assume that freshly generated glyoxal should react with phosphoranes in a general synthesis of enals. This is illustrated in eq 21. Since the glyoxal has two reactive carbonyl groups, products arising from bis-addition to the carbonyl groups are likely to occur, i.e. RR'C=CH-CH=CRR'.



VII

(21)

Monomeric glyoxal was generated by pyrolysis of "glyoxal trimer" (MC&B) in the presence of phosphorus pentoxide. essentially according to the procedure of Horwood, who studied the kinetics of the decomposition of glyoxal gas.[20] The yellow-green gas was passed through a tube containing potassium hydroxide pellets and was collected at -78°C in dry tetrahydrofuran (THF). The pyrolysis was conducted under vacuum (water aspirator) and the weighed glyoxal was used immediately, (eq 22).



Glyoxal Trimer (MC&B)

Monomer 25-30%

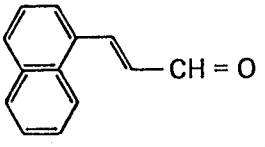
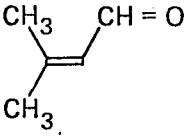
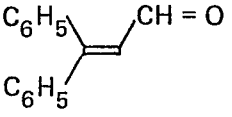
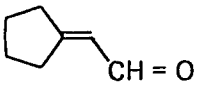
VII

(22)

Phosphorus ylids were prepared by standard techniques (see experimental section). The ylids were added slowly to a stirred solution of glyoxal VII in THF. This method of inverse addition proved very cumbersome. The yellow glyoxal solution was immediately decolorized by the red ylids and the mixture was worked up after a few hours of additional stirring. The results of these experiments are presented in Table 1.

Table 1[21a]

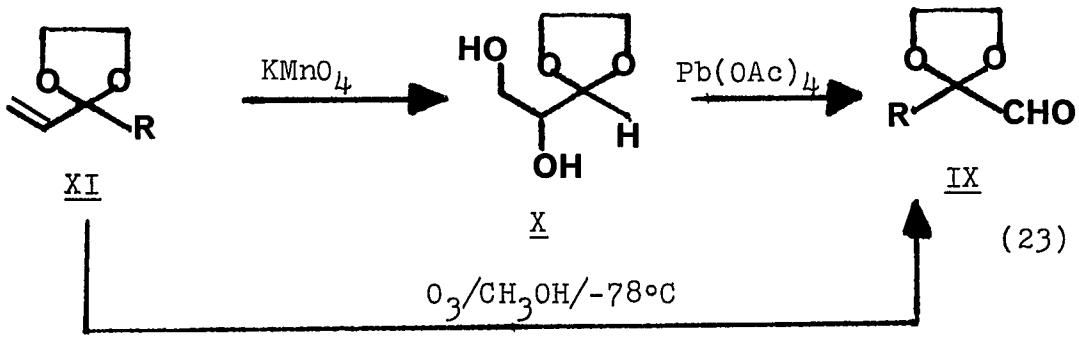
Wittig Reactions Using Monomeric Glyoxal

Entry	P-Ylid	α,β-Unsaturated Aldehyde	Yield (Isolated)
1	Benzyl -	trans-Cinnamaldehyde	39%
2	α-Naphthyl -		43%
3	iso-Propyl -		62%
4	Benzhydryl -		45%
5	Cyclopentyl -		22%

B. Monoprotectected Glyoxals And The Synthesis of Glyoxal Monodiethylacetal XV.

The poor results obtained with monomeric glyoxal VII and the experimental difficulties associated with its use, prompted a search of the literature for a monoprotected form of glyoxal that could be prepared in high yield from commercially available starting materials.

The literature revealed a number of possibilities. Faass and Hilgert prepared glyoxal monoethylene ketal IX (R=H) as a distillable liquid by lead tetraacetate oxidation of glycol X,[22] but the yield in this reaction was only 35%. Glycol X was in turn prepared in 49% yield by potassium permanganate oxidation of acrolein ethylene ketal XIa (R=H). The overall sequence is shown in eq 23.



(23)

The ketal IX (R=H) polymerizes on standing.

A further literature reference refers to this compound as an unisolated intermediate in the synthesis of methyl 1,3-dioxolane-2-carboxylate XII. The intermediate aldehyde IXa (R=H) was obtained by ozonolysis of acrolein ethylene ketal XIa (R=H) in methanol.[23a] This experiment actually proved to be the key in the later choice of glyoxal monodiethylacetal as the generalized aldehyde component (vide infra). The ozonolysis sequence is illustrated in eq 23.

Similarly, Hahn and Muxfeldt have reported the ozonlysis of the ethylene ketal of methyl vinyl ketone XIb (R=CH_3). They obtained the monoprotected methylglyoxal IXb (R=CH_3), (eq 23).[23b]

Fischer and Taube[24] and Severin[25] have made use of the monophenylhydrazone XIII and the monomethylphenylhydrazone XIV of glyoxal. However, these compounds are available only in 52% and 49% yields respectively, which makes them considerably less attractive as the generalized aldehyde component. Furthermore, hydrolysis of the hydrazone back to the carbonyl group often requires harsher conditions compared to the analogous acetal or ketal.

$OHC-CH=N-NH-C_6H_5$ — XIII

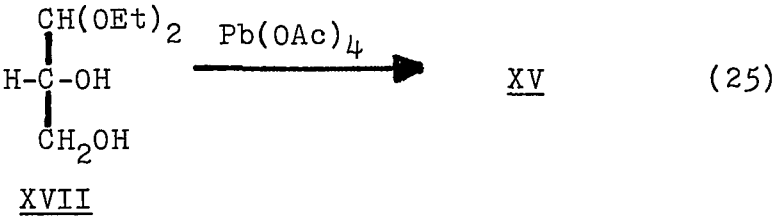
$OHC-CH=N-N(CH_3)-C_6H_5$ — XIV

In 1903 C. Harries reported the preparation of glyoxal monodiethylacetal XV by ozonolysis of acrolein diethylacetal XVI in water and work up with potassium carbonate, (eq 24).[26]

$$H_2C{=}CH\text{-}CH(OEt)_2 \xrightarrow{O_3/H_2O} OHC\text{-}CH(OEt)_2 \qquad (24)$$

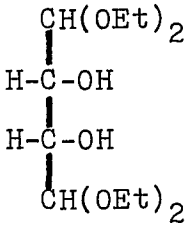
XVI XV

No yield or experimental verification was given except that a bis-phenylhydrazone was prepared. Later this work was repeated by Fischer and Baer.[27] They could not obtain the monoacetal XV by the Harries procedure.[25] They also tried ozonolysis in ethyl acetate and dichloromethane with work up using palladium on barium carbonate, but without success. They succeeded in preparing the monoacetal XV by oxidative cleavage of glyceraldehyde diethylacetal XVII with lead tetraacetate in 50-53% yield. Modern syntheses[33a, 34, 35] of the monoacetal XV by this technique have given consistent yields of 30-40%. The Fischer-Baer synthesis is shown in eq 25.



XVII

Fischer and Taube mentioned obtaining the same monoacetal XV by lead tetraacetate oxidation of tartaric aldehyde tetraethylacetal XVIII, (eq 26).[28]



$$\xrightarrow{Pb(OAc)_4} \quad \underline{XV} \qquad (26)$$

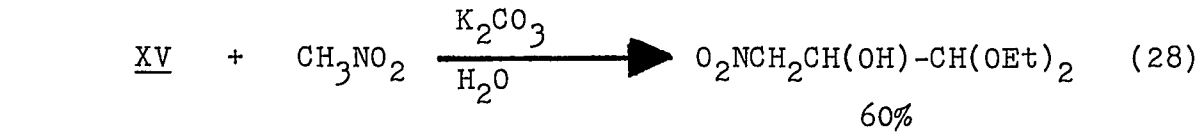
XVIII

Fischer and Baer reported that the compound polymerized readily upon standing, but that the monomer could be regenerated by pyrolysis (distillation). They obtained a bis-phenylhydrazone as a derivative, and found that the monoacetal XV would undergo the Cannizzaro reaction in cold alkali. They obtained a good elemental analysis and also attempted molecular weight determinations of the monomer and the polymer by cryoscopic methods. The results for the polymer were not accurate. Finally, they prepared the Grignard adduct of the monoacetal XV with methyl magnesium bromide. The resulting 2-hydroxypropanal diethylacetal gave a satisfactory elemental analysis, (eq 27).

$$\underline{XV} + CH_3MgBr \longrightarrow CH_3CH(OH)\text{-}CH(OEt)_2 \qquad (27)$$

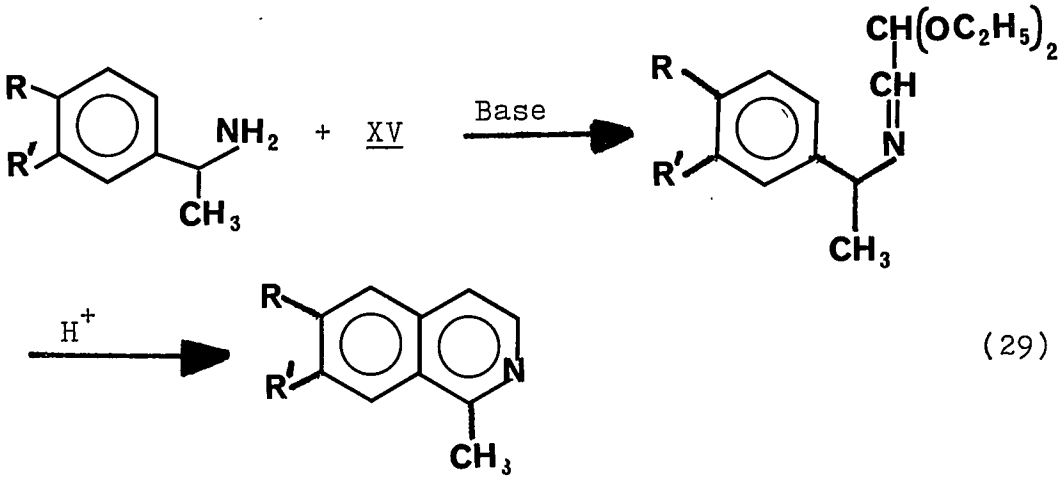
XIX

Glyoxal monoacetal XV has been used very infrequently since its initial report in 1903. Fischer and co-workers examined the aldol condensation of XV with nitromethane, (eq 28).[30]



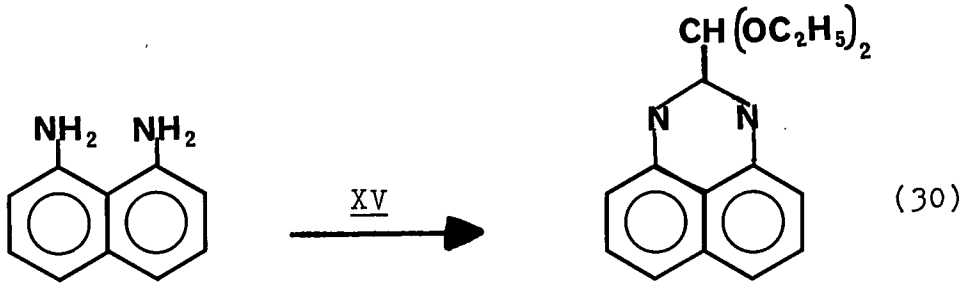
(28)

The monoacetal XV was used in a modification of the Pomeranz-Fritsch isoquinoline synthesis, (eq 29).[31]

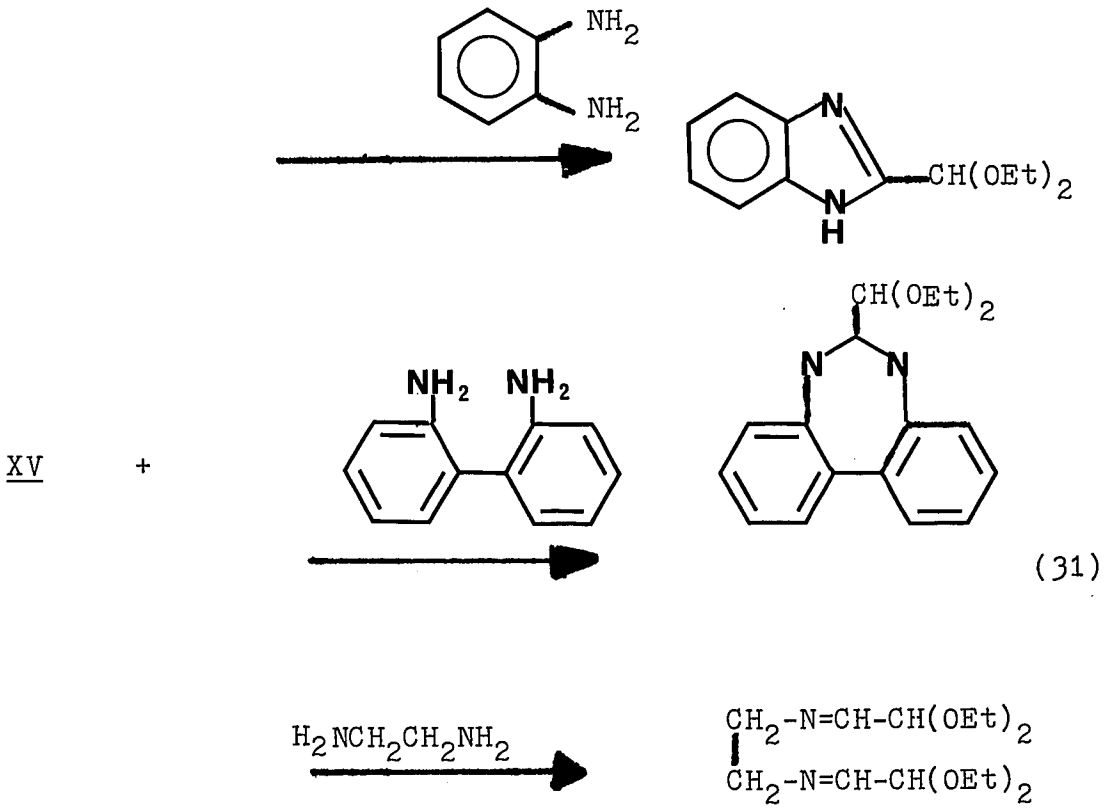


(29)

N. Vinot used the monoacetal XV in a condensation with 1,8-diaminonaphthalene[32a] and other aromatic and aliphatic diamines[32b] as illustrated in eqs 30 and 31.

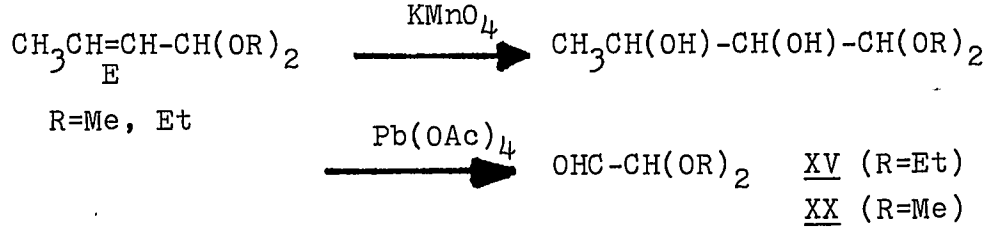


(30)



(31)

Russian workers have reported a synthesis of the monodiethylacetal XV and monodimethylacetal XX,[33a] (eq 32), by a procedure similar to that of Fischer and Baer,[27] and then used the acetals in Wittig reactions with some stabilized ylids as illustrated in eq 33.[33b]



(32)

$$\underline{XV} + \underset{\underline{I}}{OHC\text{-}CH{=}P(C_6H_5)_3} \longrightarrow \underset{E}{OHC\text{-}CH{=}CH\text{-}CH(OEt)_2} \quad (33)$$

Meyers and co-workers used the monoacetal XV in a Wittig condensation with carboethoxy methylenetriphenyphosphorane XXI, (eq 34).[34] These workers specifically point out the difficulty in obtaining usable quantities of the monoacetal XV by the oxidation procedure using lead tetraacetate.

$$\underline{XV} + \underset{\underline{XXI}}{(C_6H_5)_3P{=}CH\text{-}COOEt} \longrightarrow \underset{E}{EtOOC\text{-}CH{=}CH\text{-}CH(OEt)_2} \quad (34)$$

Battersby and co-workers used XV in an intermediate step in the synthesis of scoulerine.[35]

Glyoxal monodiethylacetal XV appeared to be a useful formylolefination synthon if its accessibility could be improved. Therefore, the ozonolysis of the commercially available acrolein diethylacetal XVI was reexamined. When XVI was ozonized at -78°C in dry methanol, and the intermediate ozonide worked up with dimethyl sulfide,[36] a very high yield, ca. 90-97% of 93-100% pure glyoxal monoacetal XV was obtained as a monomer. The important aspect of the ozonolysis seems to be the solvent, methanol, which may serve as a scavenger of the reactive formaldehyde by converting it into its stable hemiacetal. Once volatiles are removed under vacuum, the monoacetal XV can be isolated by direct distillation, (eq 35).

$$H_2C{=}CH\text{-}CH(OC_2H_5)_2 \xrightarrow[2.\ CH_3SCH_3/0\text{-}20^\circ C]{1.\ O_3/CH_3OH/-70^\circ C} OHC\text{-}CH(OC_2H_5)_2 \qquad (35)$$

XVI XV

With mole scale quantities of the monoacetal XV now readily available, an examination of its utility as a formyl-olefination reagent could now be studied in detail.

C. Synthesis Of α,β-Unsaturated Aldehydes From Glyoxal Monoacetal XV.

A comprehensive study of the Wittig reaction between glyoxal monodiethylacetal XV and various phosphoranes was examined in order to ascertain whether XV indeed could serve as a general formylolefination reagent in the synthesis of α,β-unsaturated aldehydes. Three general classes of ylids were studied: 1. Benzylic and allylic phosphoranes; 2. Primary and secondary phosphoranes; 3. Stabilized phosphoranes. Different conditions were used for each class. The results from these studies are exemplified in the following sections.

1. Benzylic and Allylic Phosphonium Salts.

During the course of this investigation the optimum conditions for the reaction of benzyl or allyl-stabilized phosphonium salts were determined to be an *in situ* method with dimethylformamide (DMF) as the solvent and lithium ethoxide or methoxide as the base. The base was added slowly to a mixture of the phosphonium salt and the monoacetal XV. Yields were generally high using this procedure (Table 2). The intermediate α,β-unsaturated acetals were usually not isolated because ^{1}H-NMR showed they were mixtures of E and Z isomers. The crude acetals were hydrolyzed with dilute hydro-

chloric acid (HCl) in tetrahydrofuran (THF). Using these reaction conditions secondary phosphonium salts were found to be generally unreactive (Table 2, Entries 11 and 12 are exceptions). The general reaction is depicted in eq 36 and the results are shown in Table 2.

(36)

After hydrolysis the aldehydes that possess stereochemistry about the olefin group were always found to be trans (E). In all cases the vinylic protons exhibited ^{1}H-NMR coupling constants of 15-16 Hz.

Table 2

Wittig Reactions With Glyoxal Monoacetal XV, In Situ Procedure.

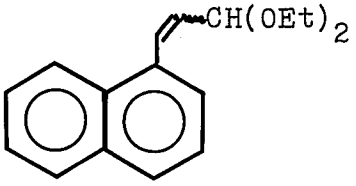
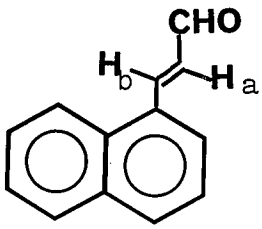
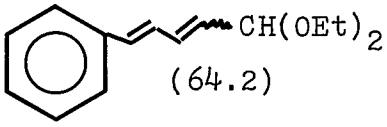
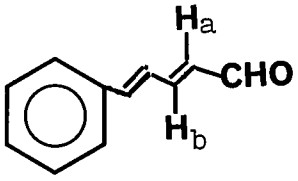
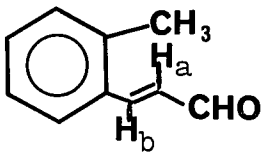
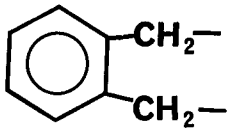
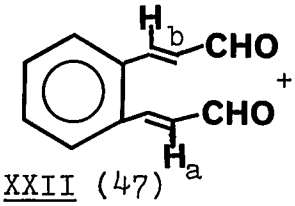
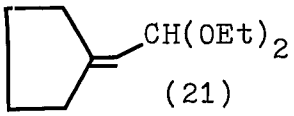
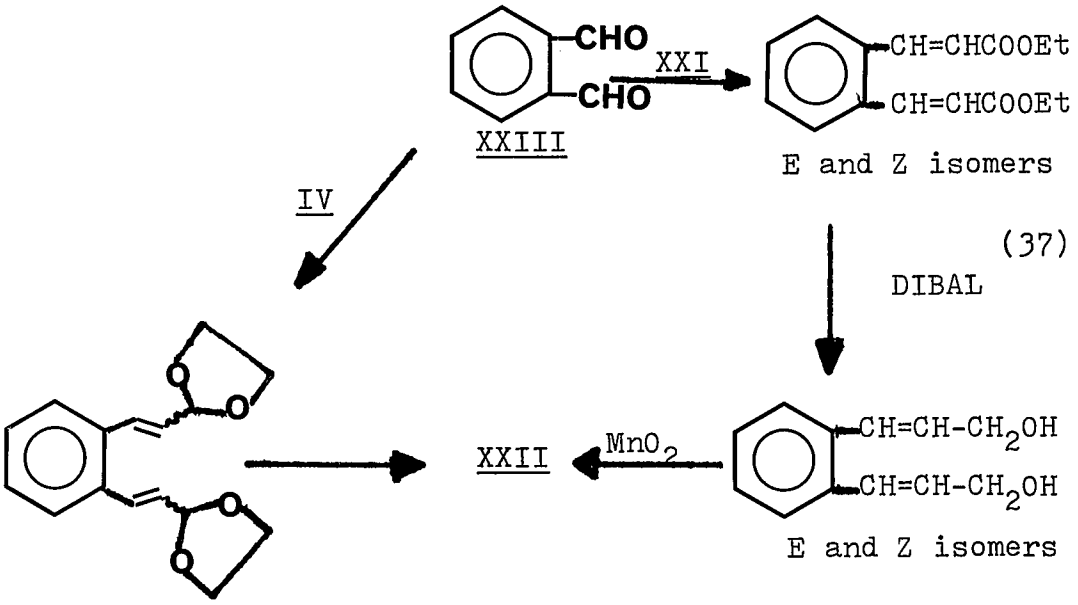
Entry	P-Salt	Acetal(Yield %)	Aldehyde(Yield %)
1	Benzyl-	-	Cinnamaldehyde (65)
2	Benzhydryl-	-	Diphenylacrolein (54)
3	α-Naphthyl-	 (90.6)	 (81)
4	Cinnamyl-	 (64.2)	 (93.2)
5	Isobutenyl-	-	$(CH_3)_2C{=}CH{-}CH{=}CHCHO$ (E) (73)
6	o-Methylbenzyl-	-	 XXV (89.2)
7	 VIIIa	 XXII (47)	+ XXV (21)

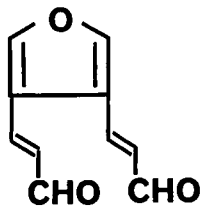
Table 2 (Continued)

Entry	P-Salt	Acetal(Yield %)	Aldehyde(Yield %)
8	Ethyl-	-	(E)-2-Butenal (65)
9	Pentyl-	-	(E)-2-Heptenal (35)
10	Hexyl-	-	(E)-2-Octenal (28)
11	Cyclopentyl-	 (21)	
12	Isopropyl-	$(CH_3)_2C{=}CH{-}CH(OEt)_2$ (9.5)	

Entry 7 represents a facile synthesis of 1,2-bis(2-formylethenyl)benzene XXII, a molecule previously synthesized by Sondheimer and co-workers by more cumbersome methods.[37] The first method involved condensation of ortho-phthalaldehyde XXIII with carboethoxymethylenetriphenylphosphorane XXI, reduction of the diester with diisobutylaluminum hydride (DIBAL) to the diol, and oxidation of the diol to the dial XXII with manganese dioxide, (eq 37). The second simpler approach involved the in situ reaction of XXIII with 1,3-dioxolan-2-ylmethyltriphenylphosphonium bromide IV[15e] with lithium ethoxide as the base, (eq 37).



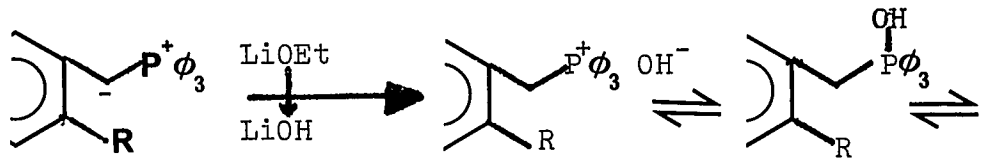
Dial XXII has been used in the synthesis of annulenes[37] and dials of type XXIV have been used in syntheses of annuleno-annulenes.[38]



XXIV

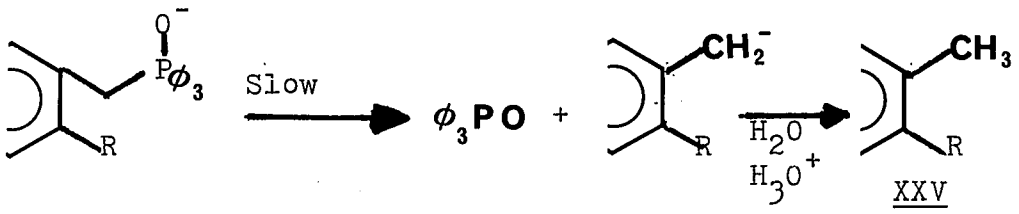
The dial XXII was separated from the major impurity, 1-methyl-2-(2-formylethenyl)benzene XXV by crystalization, (Table 2 Entry 7). The latter compound was purified by distillation and was compared with a sample prepared by independent synthesis using our method, (Table 2 Entry 6). The compounds were identical in all respects. The formation of

XXV from the ortho-xylylenebisphosphonium salt VIIIa can be rationalized as a decomposition of a phosphonium hydroxide, resulting from basic work up of the reaction.[39] This concept is presented in eq 38.



R= CH=CH-CH(OEt)$_2$
E and Z

(38)

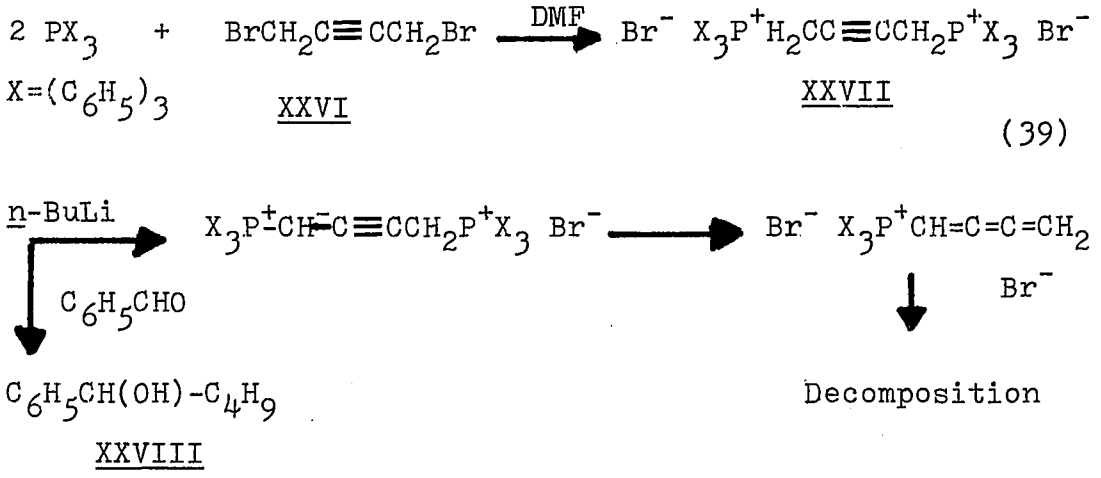


XXV

R= CH=CH-CHO
E

We investigated the reaction of glyoxal monoacetal XV with the bis-ylid derived from 2-butyne-1,4-bisphosphonium salt XXVII as a route to molecules with potential in macrocycle and annulene synthesis. The reaction of 1,4-dibromo-2-butyne XXVI with two moles of triphenylphosphine in dry DMF produced the desired bisphosphonium salt XXVII. In preliminary experiments the bis-ylid from this salt, formed under various conditions, failed to react with benzaldehyde. The only reaction observed was the nucleophilic addition of n-butyllithium to benzaldehyde forming 1-phenylpentan-1-ol XXVIII. Apparently, the bis-ylid formed under the conditions inves-

tigated was not stable and may have decomposed via a butatriene route, (eq 39).



(39)

2. Primary And Secondary Phosphonium Salts.

The ylids of primary and secondary alkyl phosphonium salts were generated in either THF, ether, or hexane with either n-butyllithium, or phenyllithium. These preformed ylids were generally stirred overnight at ambient temperature and then allowed to react with freshly distilled glyoxal monoacetal XV (10-20% excess). The reaction mixtures were stirred for two hours, then two to three equivalents of solid potassium tert-butoxide were added, stirring was continued for an additional three hours and the reactions were worked up in a standard manner (see experimental section).

Potassium tert-butoxide was added to facilitate the closure of the intermediate betaine. The principles involved were developed by Schlosser and Christmann.[40a] The lithium coordinated intermediate betaine XXIX was found to rapidly exchange lithium for potassium when potassium tert-butoxide was added. The potassium-coordinated betaine was found to extrude KX (X=halogen), leaving the ylid "salt free" XXX.[40b] Salt-free ylids were shown to close more rapidly to the olefin product and the yields of olefin were consistently higher using this technique.[40a, b] These principles are shown in eq 40.

Table 3 presents these results.

$$Y_3P^{+}-C^{-}RR' \cdots LiX + R''CHO \longrightarrow Y_3^{+}P-CRR'-CHR''O^{-} \cdots LiX$$

$Y = (C_6H_5)_3$

XXIX

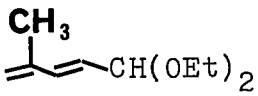
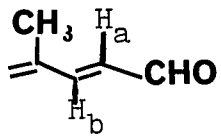
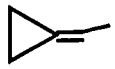
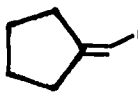
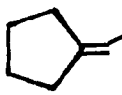
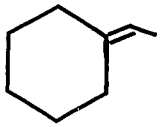
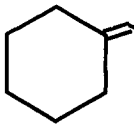
(40)

$$\xrightarrow[\substack{-KX \\ -LiO^{t}C_4H_9}]{KO^{t}C_4H_9} Y_3^{+}P-CRR'-CHR''O^{-} \xrightarrow{-Y_3PO} RR'C=CHR''$$

"salt free" XXX

Table 3

Wittig Reactions With Glyoxal Monoacetal XV, Preformed Ylids.

Entry	P-Salt	Acetal(Yield %)**	Aldehyde(Yield %)*
1	Isopropyl-	3-Methyl-2-butenal diethylacetal (63)	3-Methyl-2-butenal (79)
2	Hexyl-	2-Octenal diethyl-acetal (83)	(E)-2-Octenal (89)
3	Isopentyl-	5-Methyl-2-hexenal diethylacetal (42)	5-Methyl-(E)-2-hexenal (71), 60% when acetal not isolated.
4	2-Methyl-2-propenyl-	 (21)	 (15)
5	Cyclopropyl-	 (73) XXXI	-
6	Cyclobutyl-	 (68) XXXII	-
7	Cyclopentyl-	 (69)	 (78)
8	Cyclohexyl-	 (47)	 (93)
9	Benzyl-	-	t-Cinnamaldehyde (45)

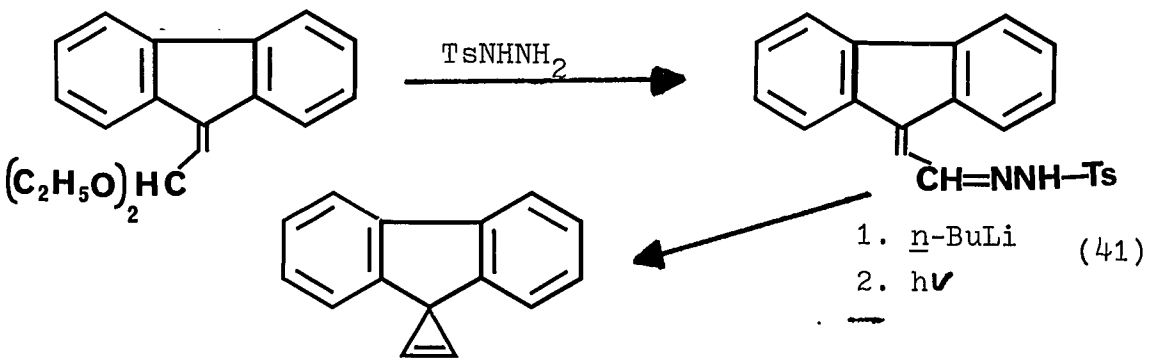
* Isolated from the acetal, ** Mixture of isomers where applicable

Entry 5 represents the first synthesis of α-cyclopropylidene acetaldehyde diethylacetal and nicely complements the recently published results of Conia and co-workers,[41] who have synthesized other α-cyclopropylidene compounds by the Wittig reaction of cyclopropylidenetriphenylphosphorane with α-ketoketals and α-ketoaldehydes, other than XV. Compound XXXI upon acid hydrolysis yielded a very unstable α,β-unsaturated aldehyde which decomposed after one night in the freezer. The analogous cyclobutylidene compound XXXII also yielded an unstable α,β-unsaturated aldehyde.

3. Stabilized Phosphoranes.

Glyoxal monoacetal XV was allowed to react in dry benzene, toluene, or para-xylene with various stabilized ylids. The results of these experiments are presented in Table 4.[21b]

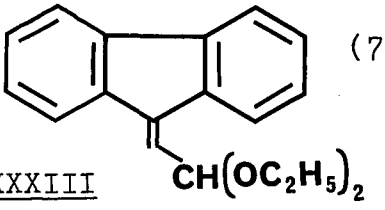
Fluorenylidene diethylacetal (Table 4, Entry 4) XXXIII is the precursor for the theoretically interesting dibenzospiro[2.4]heptatriene XXXIV, prepared by K. Grohmann according to eq 41.[42]



(41)

Table 4

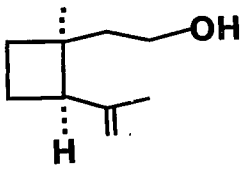
Wittig Reactions With Glyoxal Monoacetal XV, Resonance Stabilized Ylids.

Entry	P-Ylid	Acetal(E Isomer only) (Yield %)
1	EtOOCCH=	$(C_2H_5O)_2CH-CH=CH-COOEt$ (73)
2	$CH_3\overset{O}{\overset{\|}{C}}-CH=$	$(C_2H_5O)_2CH-CH=CH-\overset{O}{\overset{\|}{C}}-CH_3$ (74)
3	$EtOOCCH_2-\overset{O}{\overset{\|}{C}}-CH=$	$(C_2H_5O)_2CH-CH=CH-\overset{O}{\overset{\|}{C}}-CH_2-COOEt$ (40)
4	Fluorenyl-	 (75) XXXIII
5	OHC-CH= I	$(C_2H_5O)_2CH-CH=CH-CHO$ (68) XXXV
6	OHC-CH= (2.2 Moles) I	$(C_2H_5O)_2CH-CH=CH-CH=CH-CHO$ XXXVI (52)
7	OHC-CH= (3.3 Moles) I	$(C_2H_5O)_2CH-CH=CH-CH=CH-CH=CH-CHO$ XXXVII (36)

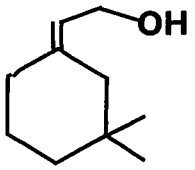
Treatment of glyoxal monoacetal XV with one mole of formylmethylenetriphenylphosphorane I cleanly formed fumaric dialdehyde monodiethylacetal XXXV, (Entry 5).[33a] This compound with a newly formed reactive aldehyde group should, in theory, be able to react with another mole of formylmethylenetriphenylphosphorane I. In the event, XV was allowed to react with 2.2 moles of I and cleanly formed muconaldehyde monoacetal XXXVI, (Entry 6). This principle was carried through in entry 7 with 3.3 moles of I, cleanly yielding 2,4,6-octatrienedial monodiethylacetal XXXVII. This homologative technique can quickly cause a chain extension (enalation) of a phosphorane like I to a conjugated olefinic system with monoprotected dialdehyde groups. There are no other obviously easy ways of accomplishing this type of transformation. Since the dialdehyde can be isolated in its monoprotected form, selective reactions at the free aldehyde group can be used for further synthetic elaboration of these molecules.

4. Attempted Synthesis of The Cyclohexyl Components of The Pheromone of The Boll Weevil.

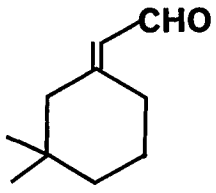
(+)-Cis-2-isopropenyl-1-methylcyclobutaneethanol (Grandisol) XXXVIII, (Z)-3,3-dimethyl-$\Delta^{1,\beta}$-cyclohexaneethanol XXXIX, (E)-3,3-dimethylcyclohexylidene acetaldehyde XL, and (Z)-3,3-dimethylcyclohexylidene acetaldehyde XLI make up the aggregate sex pheromone of the male boll weevil (Anthonomus grandis Boheman).[43] A number of syntheses of the cyclohexyl components of this pheromone have appeared.[44] Compounds XL and XLI appear to be ideally suitable for preparation from glyoxal monoacetal XV and an appropriate Wittig reagent.



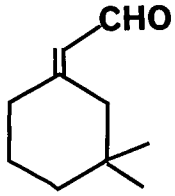
XXXVIII



XXXIX



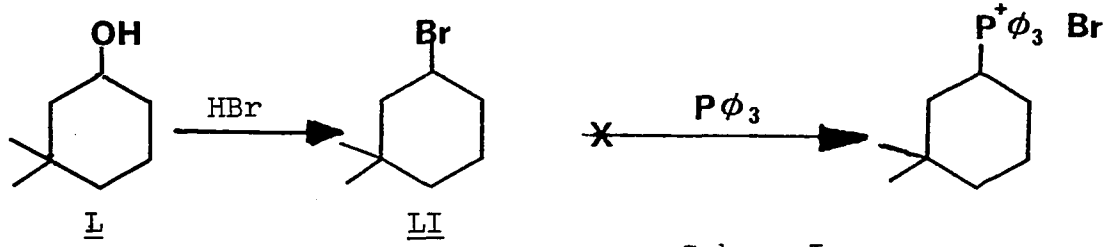
XL



XLI

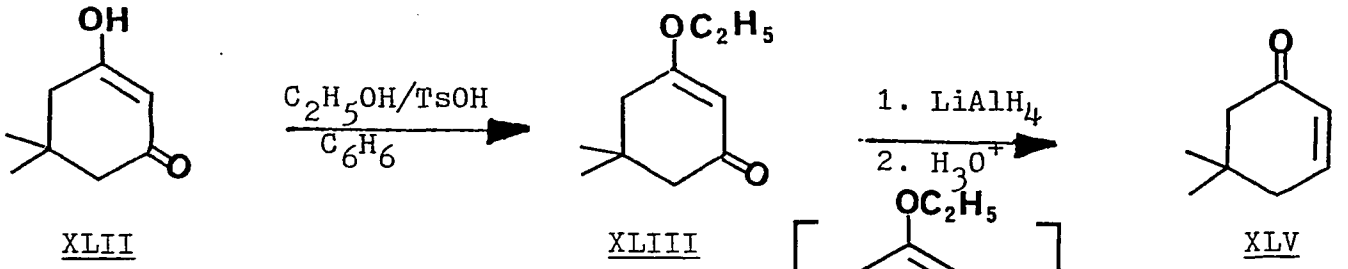
The seemingly most direct approach to these compounds would invole the Wittig reaction between 3,3-dimethylcyclohexanone and formylmethylenetriphenylphosphorane I. Unfortunately, since I does not react with ketones, this approach can not be used.

The next obvious approach to these compounds would in-

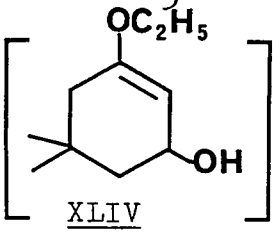


L LI (42)

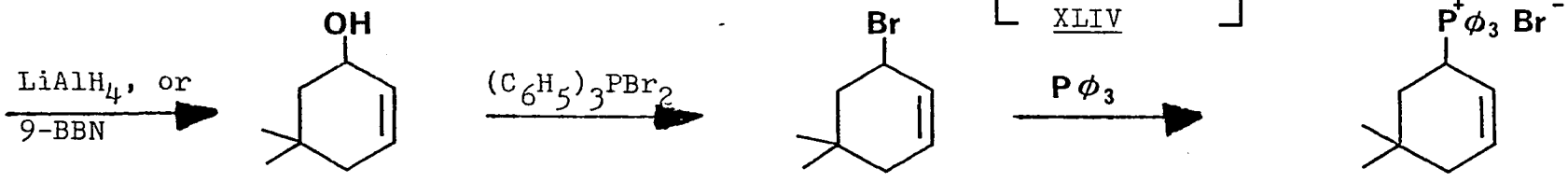
Scheme I



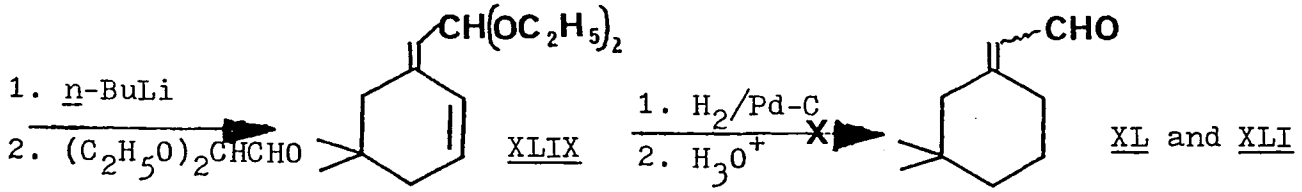
XLII XLIII XLV



XLIV



XLVI XLVII XLVIII



XLIX XL and XLI

volve the Wittig reaction between 3,3-dimethylcyclohexylidene-triphenylphosphorane and glyoxal monoacetal XV. The commercially available 3,3-dimethylcyclohexanol L was converted to the known cyclohexyl bromide LI by the technique of Fraenkel et al.[48] Bromide LI was found to be unreactive with triphenylphosphine, (eq 42). This result was not completely unexpected as an examination of models indicated that the dimethyl groups cause a severe steric interaction with the incoming triphenylphosphine. Use of the allylic bromide XLVII was expected to diminish this steric effect by flattening the cyclohexyl ring. In addition allylic bromide XLVII would be expected to react faster in nucleophilic substitution, i.e., in phosphonium salt formation, than cyclohexyl bromide LI. Therefore, the synthesis of unknown allylic bromide XLVII became the next immediate objective.

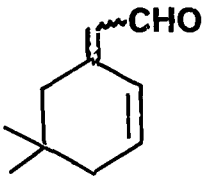
5,5-Dimethylcyclohexenone XLV was synthesized by known techniques.[45] The enone XLV was reduced either with lithium aluminum hydride (LAH),[45] or with 9-borabicyclo(3.3.1)nonane (9-BBN).[46] The LAH reduction gave the known allylic alcohol XLVI in yields of 90-92% with a purity of 90-93% by gas chromatography (GC). 9-BBN produced alcohol XLVI in 93% yield with a GC purity of 97%.

The allylic alcohol XLVI was then converted into the allylic bromide XLVII using triphenylphosphine dibromide.[47]

The resulting unknown allylic bromide gave satisfactory spectroscopic data (^{1}H-NMR, IR) and the compound was pure by gas and thin layer chromatographic analysis. The allylic bromide XLVII was allowed to react with triphenylphosphine at approximately 110°C overnight (neat). Initially, the resulting syrup refused to crystallize. In the hope of producing a crystalline phosphonium salt, the crude bromide XLVIII was dissolved in aqueous sodium or potassium iodide. This resulted in a very poor yield of crystalline phosphonium iodide XLVIIIa which, however, gave a satisfactory elemental analysis. A crystalline tetrafluoroborate XLVIIIb could also be made, in better yield, by dissolving the crude bromide XLVIII in aqueous sodium tetrafluoroborate with added fluoroboric acid. Finally, the crude bromide could be made to crystallize as a glass by very slow cooling of the reaction flask. Unfortunately, all attempts at recrystallizing the phosphonium salt XLVIII failed. Therefore, the crude crystalline phosphonium bromide XLVIII was used in all subsequent Wittig reactions.

The phosphonium salt XLVIII was allowed to react with n-butyllithium in dry hexane and the mixture was stirred for at least three hours. This cleanly produced the ylid as a deep red solution. Excess glyoxal monoacetal XV was then added resulting in immediate decolorization of the ylid. The mixture was worked up in the usual way (see experimental section). The dieneacetal XLIX could be isolated by column

chromatography or distillation; Howver, the purification process always resulted in some decomposition as shown by ^{1}H-NMR. The acetal XLIX could be hydrolyzed to a mixture of the diene aldehydes LII. Unfortunately, the last step in the synthesis of XL and XLI, the catalytic reduction of XLIX or LII failed. Hydrogenation of XLIX or LII using 10% palladium on charcoal in absolute ethanol failed to give any of the desired compounds, but instead returned unchanged starting material. The entire sequence is outlined in Scheme I.



LII

5. Knoevenagel Reaction of Glyoxal Monoacetal XV.

Besides its use in the Wittig reaction, glyoxal monoacetal XV may also be used in typical aldol condensations. Specifically, the reaction of XV with dimethyl malonate LIV in a Knoevenagel reaction was investigated. The method used a Lewis acid catalyst according to the procedure of Lehnert.[49] Acetal LIII was obtained in an unoptimized distilled yield of 58% and the compound gave a satisfactory ^{1}H-NMR spectrum, (eq 43).

$$\underline{XV} + \underset{\underline{LIV}}{CH_2(COOCH_3)_2} \xrightarrow[THF/N_2/0°C]{TiCl_4/C_5H_5N} \underset{\underline{LIII}}{(H_3COOC)_2C{=}CH{-}CH(OEt)_2} \qquad (43)$$

Chapter Three

Experimental Section

General Comments. Melting points were taken in open capillary tubes with a Buchi or meltemp apparatus and are uncorrected. Boiling points are uncorrected. Infrared spectra (IR) were recorded on Perkin-Elmer 137 or Beckman 521 spectrophotometers. Ultraviolet spectra (UV) were measured on a Cary 14 spectrophotometer. Proton nuclear magnetic resonance spectra (NMR) were measured at 60 MHz on Varian A60A or Perkin-Elmer R-24B spectrometers with tetramethylsilane as internal reference (δ = 0). Carbon-13 nuclear magnetic resonance spectra (^{13}C-NMR) were measured on a JEOL PS/PFT-100 spectrometer in chloroform-d with TMS as internal reference. Gas chromatograms - mass spectrums (GC-MS) were recorded on a Finnagan 3003 at Cornell University, Ithaca, New York. Gas chromatograms were obtained on a Hewlett-Packard 5700A gas chromatograph using a 6'x$\frac{1}{4}$" glass column packed with OV-17 on chromosorb W. Ozonolyses were performed on a Ozone Research and Equipment Corporation ozonator (model OZV9-0). Microanalyses were performed by Galbraith Laboratories Inc., Knoxville, Tenn. Analytical and preparative layer chromatography were performed on plastic and glass plates purchased from Brinkmann Instruments Inc. Basic and neutral alumina for column chromatography was purchased from ICN Pharmaceuticals Inc. and was deactivated with water. Silica gel was purchased from Brinkmann Instruments Inc.

Extraction solvents were generally of reagent quality. Reaction solvents were dried as follows: Acetonitrile,

benzene, carbon tetrachloride, chloroform, toluene, and p-xylene were distilled from phosphorus pentoxide. Hexane was distilled from phosphorus pentoxide and then from sodium. Ethyl acetate, dimethyl sulfoxide (DMSO), dimethoxyethane, and dimethylformamide (DMF) were distilled from calcium hydride. Tetrahydrofuran (THF) was distilled under nitrogen from lithium aluminum hydride (LAH) or the potassium ketyl of benzophenone. Anhydrous ether was purchased from Fisher Scientific Co. or Aldrich Chemical Co. and used as is. n-Butyllithium and phenyllithium were purchased from Alfa Inorganics. Potassium tert-butoxide was purchased from Aldrich Chemical Company and added to reactions as the solid. Cinnamaldehyde was purchased from Eastman Kodak Co. Sodium and lithium were washed with petroleum ether before use. Reactions run at ambient temperature refer to a room temperature generally between 23-25°C.

1. Preparation of Monomeric Glyoxal VII,[16,20]

A 50 mL round bottomed flask was charged with ca. 5 g (0.0352 mole) of phosphorus pentoxide and ca. 10 g of "glyoxal trimer" (MC&B). The flask was heated with a Bunsen burner under water aspirator vacuum and the yellow-green gas so produced was passed through potassium hydroxide pellets, then into 100 mL of frshly distilled THF maintained at -70°C in a three necked 500 mL round bottomed flask. This procedure produced 2.53 g (25%) of monomeric glyoxal VII. The yellow glyoxal solution was then treated immediately with the desired ylid by the method of inverse addition.

2. Preparation of trans-Cinnamaldehyde (Table 1, Entry 1):

A three necked 500 mL Schlenk tube fitted with an outlet at the bottom of the apparatus and jacketed by a 1 L beaker was charged with 8.67 g (0.02 mole) of benzyltriphenylphosphonium bromide[77] and ca. 200 mL of dry THF, maintained under an inert atmosphere at 0-5°C. n-Butyllithium (2.0 M, 13 mL, 0.026 mole) was added dropwise over twenty minutes to the stirred salt. The resulting red ylid was stirred for 2 h at ambient temperature and then added to the rapidly stirred solution of monomeric glyoxal VII at 0°C. The yellow glyoxal solution was immediately decolorized by the ylid and stirring was continued overnight. The suspension was poured onto ca. 1 L of cold water and volatiles were removed in vacuo. The remaining suspension was extracted with ether (3x 200 mL) and the combined ether extracts were washed with water. The ether extract was dried ($MgSO_4$) and concentrated in vacuo. The remaining solid was chromatographed on alumina II with petroleum ether and later with 30% benzene/petroleum ether. Trans, trans-1,4-diphenyl-1,3-butadiene (1.02 g, 24.75%) was isolated; mp(95% ethanol) 152-153°C, (Lit.[50] 152-153°C). IR(KBr); 3000, 1600, 1590, 1490, 1445, 1070, 995, 910, 825, 740 $cm.^{-1}$ NMR(CH_2Cl_2); δ 6.77 (m, 4H), 7.30 (m, 10H). Continued elution afforded 0.72 g (27.2%) of trans-cinnamaldehyde, identical in all respects (IR, NMR, and TLC) with authentic material.

3. Preparation of Cyclopentyltriphenylphosphonium Bromide:[51]

A 500 mL round bottomed flask fitted with a reflux condenser and drying tube was charged with 78.7 g (0.30 mole) of triphenylphosphine and 100 g (0.74 mole) of bromocyclopentane. The mixture was heated at 150-160°C for ca. 60 h. The resulting solid was recrystalized from methanol-water to afford 97.54 g (79%) of pure salt; mp 265.5-268°C, (lit.[51] mp 263°C).

4. Preparation of Cyclopentylidene Acetaldehyde (Table 1, Entry 5):[66]

The acetaldehyde was prepared in a similar manner as trans-cinnamaldehyde. Cyclopentyltriphenylphosphonium bromide (13.65 g, 0.033 mole) was suspended in 200 mL of dry ether. n-Butyllithium (2.3 M, 17 mL, 0.039 mole) was added dropwise to the rapidly stirred suspension. The ylid was added to 1.95 g (0.034 mole) of monomeric glyoxal and stirred overnight. The reaction was worked up as before. The crude product was chromatographed on alumina II and eluted with petroleum ether and later petroleum ether/benzene (1:1) affording 0.798 g (22%) of cyclopentylidene acetaldehyde as a yellow unstable oil.

IR(neat); 3040, 2970, 2760, 1675, 1640 cm^{-1}

NMR(CCl_4); δ 1.6-2.0 (m, 4H), 2.32-3.0 (m, 4H), 5.92 (m, 1H),

9.82 (d, 1H, J = 7.6 Hz).

5. Preparation of Glyoxal Monodiethylacetal XV:

Acrolein diethylacetal (79.87 g, 0.613 mole) and 500 mL of dry methanol were placed in a three necked 1 L round bottomed flask equipped with a magnetic stirrer, gas dispersion tube reaching to near the bottom of the flask, and a gas outlet tube connected to a U-tube filled with a potassium iodide solution. The flask was cooled to -70°C and a vigorous stream of ozone was passed through the stirred solution (ozonizer settings: flow rate 7, powerstat ca. 78 (0.65 amp), water cooling on). With these settings ca. 0.1 mole of starting material was ozonized per hour. After the reaction was complete (reaction turned a persistent blue) oxygen was bubbled through for five minutes and then nitrogen was bubbled through for the remainder of the reaction. At -70°C 51.4 g of dimethyl sulfide was added and the temperature was allowed to rise slowly overnight. The methanol was removed on a rotary evaporator (bath temperature 20-25°C). The remaining liquid was distilled to afford 75.07 g (93%) of glyoxal monoacetal, contaminated with 4% dimethyl sulfoxide. The distillation receiver must be well cooled to prevent loss of material; bp 42-48°C (15 mm), (lit.[11] bp 42-43°C (11 mm)), IR(neat); 2990, 2860, 1742, 1070 $cm.^{-1}$
NMR($CDCl_3$); δ 1.3 (m, 6H), 3.65 (m, 4H), 4.55 (d, 1H, J = 3 Hz), 9.4 (d, 1H, J = 3 Hz).

The compound slowly polymerizes (2-3 weeks in the refrigerator), but can be regenerated by vacuum distillation (pyrolysis).

6. Preparation of (2E, 4E)-5-Phenyl-2,4-pentadienal (Table 2., Entry 4):[52, 53]

A Schlenk tube fitted with a 50 mL dropping funnel was charged with 5.69 g (0.0124 mole) of cinnamyltriphenylphosphonium bromide,[71] 1.39 g (0.0105 mole) of glyoxal monoacetal, and ca. 100 mL of dry DMF under nitrogen. The dropping funnel was charged with 0.1344 g (0.0192 mole) of lithium shot and 25 mL of absolute ethanol. A reflux condenser was placed on top of the dropping funnel along with a potassium hydroxide drying tube. The lithium ethoxide was added very slowly ca. 1.5 h to the vigorously stirred salt-acetal solution, maintained at 70°C. The mixture was stirred overnight at 70°C. The solution was cooled and poured onto water and extracted with ether (2x200 mL). The ether was washed with brine, dried (K_2CO_3), and concentrated <u>in vacuo</u> to afford 3.1674 g of crude product, contaminated with triphenylphosphine oxide. The product was distilled to afford 1.564 g (64.2%) of the yellow acetal as a mixture of E and Z isomers; bp 106-110°C (0.24 mm). IR(neat); 3085, 3065, 3030, 2980, 2935, 2880, 1950, 1870, 1800, 1677, 1640, 1618, 1490, 1445, 1130, 1050, 985, 780, 745 $cm.^{-1}$

NMR(CCl_4); δ 1.17 (t, 6H, J = 7 Hz), 3.6 (m, 4H), 4.98 (d,

with fine splitting, 1H, J = 4 Hz), 5.3-6.6 (m, 4H), 7.25 (br s, 5H).

The mixture of E and Z acetals (1.564 g, 0.0067 mole) was taken up in 100 mL of THF and placed in an ice bath. Ten percent HCl (100 mL) was added and the solution was stirred for 2 h. The solution was extracted with ether, washed with $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated in vacuo to afford a yellow oil which was distilled to give the desired aldehyde, 0.9865 g (93.2%). bp 123-125°C (1.3 mm), (lit.[52] 133-134°C (1 mm)); semicarbazone, mp(ethanol) 225-226°C, (lit.[53] mp 218-218.5°C); IR(neat); 3330, 3085, 3062, 3030, 3008, 2925, 2820, 2745, 1955, 1886, 1805, 1688, 1665, 1618, 1592, 1487, 1449, 1010, 983, 785, 745 $cm.^{-1}$ NMR(CCl_4); δ 6.20 (dd with fine splitting, $1H_a$, J = 15.5, 7.5 Hz), 6.98 (m, 3H), 7.36 (m, 5H), 9.47 (d, 1H, J = 7.5 Hz).

7. Preparation of 3-[Naphthyl-(1)]-acrolein (Table 2, Entry 3):[54]

This compound was prepared using a procedure identical to experiment 6. α-Naphthylmethyltriphenylphosphonium chloride[72] (5.29 g, 0.012 mole), 1.3969 g (0.0102 mole) of glyoxal monoacetal, and 0.1388 g (0.0198 mole) of lithium wire with 25 mL of absolute ethanol were allowed to react in the usual way. Work up and distillation of the residue afforded 2.32 g (90.6%) of the desired acetal as a mixture of E and Z

isomers; bp 118-119°C, (0.12 mm).
IR(neat); 3068, 3050, 2980, 2932, 2878, 1940, 1810, 1680, 1643, 1588, 1507, 1488, 1110, 1050, 990, 780 $cm.^{-1}$
NMR(CCl_4); δ 1.09 (m, 6H), 3.52 (m, 4H), 5.05 (br d, 1H, J = 7 Hz), 5.85-6.35 (m, 1H), 6.9-7.9 (m, 8H).

The acetal (1.340 g, 0.0052 mole) was hydrolyzed with 5% HCl in THF at 0-5°C for 1 h. After the usual work up chromatography of the residue on silica gel and elution with 1% ether in benzene afforded 0.7667 g (81%) of the desired aldehyde; mp(ether) 44-46°C, (lit.[54] mp 48°C). The product could be distilled with some decomposition; bp 90-93°C, (0.18 mm); semicarbazone, mp(ethanol) 222-223°C, (lit.[54] 228°C).
IR(neat); 3340, 3070, 2825, 2735, 1940, 1815, 1675, 1625, 1610, 1575, 1510, 1125, 970, 790, 770 $cm.^{-1}$
NMR(CCl_4); δ 6.73 (dd, $1H_a$, J = 16, 7.5 Hz), 7.3-8.2 (m, 8H), 9.75 (d, 1H, J = 7.5 Hz).

8. Preparation of 2-Methylbenzyltriphenylphosphonium Bromide:[55]

A 500 mL single necked round bottomed flask was charged with 18.5 g (0.1 mole) of α-bromo-o-xylene and 26.42 g (0.1 mole) of triphenylphosphine. Dry benzene (200 mL) was added and the mixture was refluxed for 3 h. The resulting precipitate was washed well with ether and air dried. The phosphonium salt, 38.36 g (85.8%), was used without further

purification; mp 273-275°C, (lit.[55] mp 253-255°C).

9. Preparation of o-Methylcinnamaldehyde XXV (Table 2, Entry 6):[56]

This aldehyde was prepared using a similar procedure to that in experiment 6. 2-Methylbenzyltriphenylphosphonium bromide (5.4452 g, 0.0127 mole), 1.3468 g (0.0102 mole) of glyoxal monoacetal, 0.1246 g (0.0179 mole) of lithium wire, 100 mL of dry DMF and 25 mL of absolute ethanol were combined in the usual way. The reaction mixture was stirred for 3 h at 70°C and then worked up as usual. The crude acetal was not isolated. Hydrolysis of the crude acetal in THF/10% HCl (3:1) at 0-5°C for 3 h afforded the crude aldehyde. The aldehyde was isolated by Kugelrohr-type distillation, 1.3285 g (89.2%); bp 67-70°C (0.1 mm), (lit.[56] bp 115-116°C (2 mm)); Semicarbazone, mp(95% ethanol) 213.5-214.5°C, (lit. mp 216°C;[56] 217°C[57]).

IR(neat); 3070, 3035, 2970, 2940,2820, 2748, 1960, 1920, 1810, 1677, 1620, 1600, 975, 750 cm^{-1}

NMR(CCl_4); δ 2.4 (s, 3H), 6.52 (dd, $1H_a$, J = 16, 7 Hz), 7.2-7.8 (m, 5H), 9.6 (d, 1H, J = 7 Hz).

10. Preparation of Cyclopentylidene Acetaldehyde Diethylacetal (Table 2, Entry 11):

This compound was prepared using the general procedure in experiment 6. Cyclopentyltriphenylphosphonium bromide (9.5880 g, 0.0233 mole), 2.6437 g (0.0201 mole) of glyoxal-monoacetal, 0.1832 g (0.0264 mole) of lithium shot, 21 mL of absolute ethanol and 150 mL of dry DMF were combined in the usual way. The reaction was stirred for 3 h at 60-70°C. Work up and distillation of the residue afforded 0.77 g (21%) of the desired acetal; bp 50-53°C (0.38 mm)
IR(neat); 2990, 2940, 1670, 1630, 1430, 1120, 1040 $cm.^{-1}$
NMR(CCl_4); δ 1.13 (t,6H, J = 7 Hz), 1.67 (m, 4H), 2.3 (m, 4H), 3.5 (m, 4H), 4.98 (d, 1H, J = 6.3 Hz), 5.37 (m, 1H).

11. Preparation of 3-Methyl-2-butenal Diethylacetal (Table 2, Entry 12).[58]

The compound was prepared using the general procedure of experiment 6. Isopropyltriphenylphosphonium iodide[73] (5.0278 g, 0.0120 mole), 1.3253 g (0.010 mole) of glyoxal monoacetal, 0.1057 g (0.0152 mole) of lithium shot, 21 mL of absolute ethanol and 100 mL of DMF were combined as previously described and the reaction was stirred for 3 h at 60-70°C. Work up and distillation of the resulting oil afforded 0.15 g (9.5%) of the desired acetal; bp 53-55°C (12 mm), (lit.[58] bp

60-62°C (17 mm)); IR(neat); 2984, 2940, 2885, 1676, 1442, 1140, 1082, 1052 $cm.^{-1}$
NMR(CCl_4); δ 1.15 (t, 6H, J = 7 Hz), 1.72 (br s, 6H), 3.50 (m, 4H), 5.07 (d, 1H, J = 6 Hz), 5.2 (m, 1H).

12. Preparation of o-Xylylene-bis-(triphenylphosphonium bromide)?[59]

A 500 mL single necked round bottomed flask, equipped with a reflux condenser and nitrogen inlet was charged with 41.5532 g (0.157 mole) of α,α'-dibromo-o-xylene, 79.8686 g (0.3045 mole) of triphenylphosphine, and 300 mL of dry DMF. The flask was heated at 100°C for 48 h and the resulting solid was collected and washed well with ether and allowed to air dry. The product obtained, 117.36 g (94.8%) was used without further purification.

13. Preparation of 1,2-bis(2-Formylethenyl)benzene XXII (Table 2, Entry 7): [38]

The compound was prepared using the general procedure in experiment 6. o-Xylylene-bis(triphenylphosphonium bromide (8.0755 g, 0.0102 mole), 3.0882 g (0.0234 mole) of glyoxal monoacetal, 0.1573 g (0.0226 mole) of lithium shot, 27 mL of absolute ethanol, and 200 mL of dry DMF were combined as previously described at 70-80°C for 3 h. After the usual

work up the compound was isolated by crystallization from petroleum ether/ether to afford the desired dialdehyde as a pale yellow solid, 0.8842 g (46.8%); mp(ethyl acetate) 113-114°C, (lit.[38] 115-116°C);Bis-semicarbazone, mp(EtOH) 225-6°C. IR(KBr); 1680, 1650, 1600, 990, 980 $cm.^{-1}$ NMR(Acetone-d_6); δ 6.75 (dd, 2H_a, J = 16, 7.5 Hz), 6.9-7.9 (m, 4H), 8.15 (d, 2H_a, J = 16 Hz), 9.75 (d, 2H, J = 7.5 Hz).

The remaining mother liquors were combined and distilled to yield 0.3873 g (20.5%) of o-methylcinnamaldehyde XXV; bp 67-70°C (0.1 mm), (lit.[56] bp 115-116°C (2 mm)). Spectral properties in agreement with experiment 9.

14. Preparation of 5-Methyl-(E)-2-hexenal (Table 3, Entry 3):[60]

i. By direct isolation of aldehyde;

A 250 mL Schlenk tube was charged with 5.0377 g (0.0121 mole) of 3-methyl-1-butyltriphenylphosphonium bromide[74] and ca. 125 mL of dry ether under nitrogen. n-Butyllithium (2.45 M, 6 mL, 0.0147 mole) was added dropwise with stirring at 0-5°C. The ylid was stirred overnight at ambient temperature, then 1.3839 g (0.0105 mole) of glyoxal monoacetal in 10 mL of dry ether was added dropwise at ambient temperature. The red colored ylid turned a yellow-tan and the suspension was stirred for 1 h. Potassium tert-butoxide (2.3977 g, 0.0210 mole) was added and the suspension turned brown-tan.[40a] This suspension was stirred for 3 h and then poured onto cold

dilute potassium hydroxide solution and extracted with ether (2x200 mL). The ether was washed with distilled water and dried (K_2CO_3), then concentrated *in vacuo* to afford an oil. The crude acetal was taken up in THF and hydrolyzed at 0-5°C with 10% HCl for 1 h. The solution was extracted with ether (3x50 mL) and washed sequentially with $NaHCO_3$, water, and brine. The ether was dried ($MgSO_4$) and concentrated *in vacuo* to afford an oil which was distilled on a Kugelrohr-type apparatus, 0.7649 g (65.4%); bp 48-50°C (12 mm), (lit.[60] 81-83°C (50 mm)); DNP, mp(ethanol) 148-150°C, (lit.[60] 149-150°C). IR(neat); 2970, 2880, 2820, 2740, 1690, 1640, 1465 $cm.^{-1}$ NMR(CCl_4); δ 0.98 (d, 6H, J = 6 Hz), 1.7-2.4 (m, 3H), 6.08 (ddt, $1H_a$, J = 16, 7.5, 1.5 Hz), 6.87 (dt, $1H_b$, J = 16, 7 Hz), 9.35 (d, 1H, J = 8 Hz).

ii. By isolation of acetal;

Using a similar procedure as in i. 5.0011 g (0.0121 mole) of 3-methyl-1-butyltriphenylphosphonium bromide, 7.6 mL (0.0186 mole) of 2.45 M *n*-butyllithium, 1.34 g (0.010 mole) of glyoxal monoacetal, and 2.4350 g (0.0217 mole) of potassium *tert*-butoxide were combined as before and after work up the crude acetal was isolated as an oil. Distillation in a Kugelrohr-type apparatus afforded 0.7843 g (42.2%) of the desired acetal as a mixture of cis-trans isomers; bp 93-95°C (2.7 mm). IR(neat); 3035, 2970, 2940, 2870, 1658, 1463, 1120, 1052, 995 $cm.^{-1}$ NMR(CCl_4); δ 0.92 (d, 6H, J = 7 Hz), 1.16 (t, 6H, J = 7.5 Hz), 1.65 (m, 1H), 2.03 (q, 2H, J = 5.5 Hz). 4.52 (m, 4H), 5.15 (d with fine structure, 1H, J = 5 Hz), 5.5 (m, 2H).

The above acetal (0.7566 g, 0.004 mole) was hydrolyzed in the usual way to afford the crude aldehyde. This was distilled to yield 0.32 g (70.5%) of 5-methyl-(E)-2-hexenal, identical with the spectral properties in i.

15. Preparation of (E)-2-Octenal (Table 3, Entry 2):[60]

Using the general procedure of experiment 14, 5.1350 g (0.0123 mole) of hexyltriphenylphosphonium bromide,[75] 7 mL (0.0175 mole) of 2.45 M n-butyllithium, 1.38 g (0.0104 mole) of glyoxal monoacetal, 2.4462 g (0.0218 mole) of potassium tert-butoxide, and 200 mL of ether were combined in the usual way. After work up an oil was isolated, distillation of which afforded 1.66 g (83%) of the desired acetal as a mixture of cis-trans isomers; bp 42-43°C, (0.05 mm), (lit.[61] cis isomer only bp 116-118 (30 mm)).

IR(neat); 3020, 2980, 2960, 2930, 1652, 1458, 1435, 1110, 1045, 990 $cm.^{-1}$

NMR(CCl_4); δ 1.14 (t, 6H, J = 7 Hz), 0.9-1.6 (m, 9H), 2.13 (m, 2H), 3.52 (m, 4H), 5.16 (m, 1H), 5.38-5.83 (m, 2H).

2-Octenal diethylacetal (1.56 g, 0.0078 mole) was hydrolyzed for 4.5 h at ambient temperature in THF/5% HCl (1:1). Work up and distillation afforded 0.87 g (88.8%) of the desired aldehyde; bp 75-77°C (15 mm), (lit.[60] 69-71°C (9 mm)); DNP(EtOAc) mp 124-125°C, (lit.[60] mp 128°C).

IR(neat); 3035, 2965, 2935, 2865, 2820, 2740, 1690, 1630,

1460, 1145, 975 $cm.^{-1}$

NMR(CCl_4); δ 0.90 (t, 3H, J = 6 Hz), 1.1-1.8 (m, 6H), 2.33 (q, 2H, J = 6 Hz), 6.05 (ddt, $1H_a$, J = 15.5, 7.5, 1.2 Hz), 6.85 (dt, $1H_b$, J = 15.5, 7.5 Hz), 9.55 (d, 1H, J = 7.5 Hz).

16. Preparation of 3-Methyl-2-butenal (Table 3, Entry 1):[63]

A 250 mL Schlenk tube was charged under nitrogen with 9.9204 g (0.0229 mole) of isopropyltriphenylphosphonium iodide[73] and 100 mL of dry hexane, and 10 mL (0.0245 mole) of 2.45 M n-butyllithium was added dropwise at ambient temperature. The ylid was refluxed for 1 h and stirred overnight, after which 2.4439 g (0.0185 mole) of glyoxal monoacetal in 10 mL of hexane was added and the suspension was refluxed for 2 h.[62] After cooling 4.2207 g (0.0376 mole) of potassium tert-butoxide was added and the suspension was stirred for 2.5 h. The suspension was poured onto cold dilute potassium hydroxide and extracted with petroleum ether (2x150 mL). The organic phase was washed sequentially with water (2x200 mL) and brine, dried (K_2CO_3), and concentrated in vacuo. Distillation of the resulting oil afforded 1.8424 g (63%) of 3-methyl-2-butenal diethylacetal; bp 53-55°C (12 mm), (lit.[58] 60-62°C (17 mm)). Spectral properties were identical with those of experiment 11.

The acetal (1.5500 g, 0.0098 mole) was hydrolyzed in the usual manner to afford after distillation 0.63 g (79%)

of the desired aldehyde; bp 30-31°C (12 mm), (lit.[63] bp 30-32°C (12 mm)). IR(neat); 2990, 2930, 2860, 2770, 1678, 1630, 1450, 1200 $cm.^{-1}$

NMR(CCl_4); δ 2.06 (d, 6H, J = 11 Hz), 5.8 (m, 1H), 9.95 (d, 1H, J = 8 Hz); DNP, mp(EtOAc) 180-181°C, (lit.[63] mp 183-184°C).

17. Preparation of 4-Methyl-2,4-pentadienal Diethylacetal (Table 3 Entry 4):

A 250 mL Schlenk tube was charged under nitrogen with 4.2909 g (0.0122 mole) of 2-methyl-2-propenyltriphenylphosphonium chloride,[76] 150 mL of dry ether, and 7 mL (0.0177 mole) of 2.45 M n-butyllithium were combined in the usual manner at ambient temperature. The ylid was stirred overnight, then 1.3359 g (0.0101 mole) of glyoxal monoacetal in 10 mL of ether was added. The reaction was stirred for 2 h and then worked up in the usual way. The resulting oil was distilled to afford a main fraction, bp 25-32°C (0.3 mm), 0.7734 g (45.4%). The ^{1}H-NMR indicated the acetal was present, but with significant impurities. The oil was chromatographed on basic alumina III and eluted with 10% benzene/petroleum ether, affording 0.36 g (21.1%) of the pure acetal.
IR(neat); 3085, 3025, 2980, 2930, 2880, 1680, 1640,1610, 1440, 1020, 1050, 990, 885, 775 $cm.^{-1}$

NMR(CCl_4); δ 1.14 (t, 6H, J = 7 Hz), 1.83 (br s, 3H), 3.55 (m, 4H), 5.02 (br s, 2H), 5.15-6.6 (m, 3H).

The acetal was hydrolyzed at 0-5°C for 1 h in the usual way. The very sensitive aldehyde was isolated by steam distillation, but could never be freed from significant impurities. Attempted distillation of the crude aldehyde resulted in major decomposition. DNP, mp(EtOAc) 135-136°C. IR was not taken. NMR(CCl_4); δ 1.90 (s, 3H), 5.4 (br s, 2H), 6.05 (dd, $1H_a$, J = 17, 7 Hz), 7.2 (d, $1H_b$, J = 17 Hz), 9.52 (d, 1H, J = 7 Hz). There were impurities with signals at 1.0-1.5 and 3.0-5.0 ppm.

18. Preparation of trans-Cinnamaldehyde (Table 3, Entry 9):

A 250 mL Schlenk tube was charged under nitrogen with 2.0647 g (0.005 mole) of benzyltriphenylphosphonium bromide,[77] 120 mL of dry DMSO, and 0.749 g (0.0066 mole) of potassium tert-butoxide. The ylid was stirred for 3 h at ambient temperature, and 0.80 g (0.0066 mole) of glyoxal monoacetal in 10 mL of dry DMSO was added. The suspension was stirred for 3 h. After the usual work up the crude acetal was hydrolyzed in the standard manner. Chromatography of the crude aldehyde on alumina II with 20% benzene/petroleum ether afforded 0.29 g (45%) of trans-cinnamaldehyde, identical in all respects (IR, NMR, TLC) with an authentic sample.

19. Preparation of Cyclohexyltriphenylphosphonium Bromide:[64]

A 500 mL single necked round bottomed flask was charged with 78.74 g (0.3 mole) of triphenylphosphine and 97.725 g (0.606 mole) of freshly distilled bromocyclohexane. The flask was heated at ca. 140°C for 60 h under nitrogen. The resulting solid was collected and washed well with ether and air dried. This afforded 105.29 g (82.5%) of the desired salt. mp(methanol/water) 266-271°C, (lit. mp 255-259°C,[64] 267-269°C[51]).

20. Preparation of Cyclobutyltriphenylphosphonium Bromide:[65]

To a stirred suspension of 10.4304 g (0.0218 mole) of 4-bromobutyltriphenylphosphonium bromide[78] in 100 mL of dry ether was added dropwise under argon at 0-5°C 25 mL (0.045 mole) of 1.8 M phenyllithium. The ylid was stirred overnight. Hydrogen bromide gas was passed through the ylid, whereupon a gummy white solid deposited. The solid was recrystallized from water affording 5.9811 g (69.1%) of the phosphonium salt. mp 274-276°C, (lit.[65] mp 278.5-279.5°C).

21. Preparation of Cyclohexylidene Acetaldehyde (Table 3, Entry 8):[66]

The compound was prepared using the procedure outlined in experiment 16. Cyclohexyltriphenylphosphonium bromide (9.3774 g, 0.0220 mole), 10 mL (0.0245 mole) of n-butyllithium, 2.6894 g (0.0203 mole) of glyoxal monoacetal, 4.8922 g (0.0436 mole) of potassium tert-butoxide, and 200 mL of dry hexane were combined as described. Work up and distillation of the residue afforded 1.8543 g (47.3%) of the desired acetal; bp 60-65°C (0.25 mm); IR(neat); 2980, 2935, 2860, 1675, 1650, 1615, 1440, 1195, 1180, 1130, 1050 $cm.^{-1}$.
NMR(CCl_4); δ 1.13 (t, 6H, J = 6 Hz), 1.5 (m, 6H), 2.1 (m, 4H), 3.45 (m, 4H), 5.1 (m, 2H).

The acetal (1.69 g, 0.0085 mole) was hydrolyzed in the usual way to afford after distillation 0.9760 g (92.6%) of the desired aldehyde; bp 35-35°C (0.26 mm), (lit.[66] bp 58°C (1 mm)); DNP, mp(EtOAc) 192-195°C, (lit.[66] mp 201°C); semicarbazone, mp(ethanol/water) 208-210°C dec., (lit.[67] mp 210°C dec.); IR(neat); 2940, 2865, 2780, 1675, 1620, 1445, 920 $cm.^{-1}$
NMR(CCl_4); δ 1.69 (m, 6H), 2.28 (m, 2H), 2.75 (m, 2H), 5.72 (d with fine splitting, 1H, J = 7.6 Hz), 10.0 (d, 1H, J = 8 Hz).

22. Preparation of Cyclopentylidene Acetaldehyde (Table 3, Entry 7):[66]

The acetal was prepared using the general procedure in experiment 14. Cyclopentyltriphenylphosphonium bromide[51] (5.0845 g, 0.0123 mole), 7 mL (0.0172 mole) of 2.45 M n-butyllithium, and 100 mL of ether were combined as described. After overnight stirring of the ylid, 1.3904 g (0.0105 mole) of glyoxal monoacetal in 10 mL of ether was added followed 1 h later with 2.6268 g (0.0234 mole) of potassium tert-butoxide. The suspension was stirred for 2 h and then worked up in the usual manner. Distillation of the resulting oil afforded 1.26 g (68.5%) of the desired acetal; bp 50-53°C (0.38 mm); Spectral properties identical with experiment 10.

The acetal (1.23 g, 0.0066 mole) was hydrolyzed in the usual way to afford after distillation 0.5651 g (77.8%) of the desired aldehyde; bp 47-48°C (1 mm); DNP, mp(EtOAc) 185-186°C, (lit.[66] 180°C). Spectral properties identical with experiment 4.

23. Preparation of Cyclobutylidene Acetaldehyde XXXII (Table 3 Entry 6):

i. By reaction with cyclobutyltriphenylphosphnium bromide;

Phenyllithium (1.8 M, 9 mL, 0.016 mole) was added to a rapidly stirred suspension of 4.8164 g (0.0121 mole) of

cyclobutyltriphenylphosphonium bromide[65] in 125 mL of dry ether under argon. The ylid was stirred at ambient temperature overnight, then 1.3200 g (0.010 mole) of glyoxal monoacetal in 10 mL of ether was added. After 1 h, 2.51 g (0.0224 mole) of potassium tert-butoxide was added to the chalk white suspension and stirring was continued for 2 h. After the usual work up, distillation of the resulting oil afforded 1.2232 g (72%) of the desired acetal. From the ^{1}H-NMR the compound was contaminated with 4.8% biphenyl; bp 39-42°C (0.1 mm). IR(neat); 2985, 2940, 2880, 1682, 1120, 1065, 1045 cm.$^{-1}$ NMR(CCl_4); δ 1.1 (t, 6H, J = 7 Hz), 2.05 (m, 2H), 2.6 (m, 4H), 3.45 (m, 4H), 4.8 (d, 1H, J = 5.5 Hz), 5.05 (m, 1H).

The acetal (1.48 g, 0.0087 mole) was hydrolyzed in the usual way to afford, after bulb to bulb distillation, 0.5448 g (65.2%) of the desired aldehyde as an unstable oil. ^{1}H-NMR indicated that some decomposition had occurred during isolation. IR was not taken due to decomposition.
NMR(CCl_4); δ 1.3 (m, 2H), 2.2 (m, 4H), 5.72 (m, 1H), 9.5 (d, 1H, J = 7.5 Hz). There were impurities with signals at 3.1 ppm. Semicarbazone, mp(ethanol/water) 200-201°C.

ii. By reaction with 4-bromobutyltriphenylphosphonium bromide:

To a stirred suspension of 10.6404 g (0.0222 mole) of 4-bromobutyltriphenylphosphonium bromide[78] in 200 mL of dry ether was added under argon 50 mL (0.09 mole) of 1.8 M phenyllithium. The ylid was stirred overnight, then 2.71 g (0.0205 mole)

of glyoxal monoacetal in 10 mL of ether was added followed 1 h later with 5.0727 g (0.0452 mole) of potassium tert-butoxide. Stirring was continued for 3 h, and after the usual work up, the residue was chromatographed on basic alumina III and eluted first with petroleum ether. After the biphenyl was removed the elution solvent was changed to benzene and 1.4804 g (42.4%) of the desired acetal was isolated. ^{1}H-NMR indicated that ca. 4% of the acetal had hydrolyzed to the aldehyde during isolation. IR and ^{1}H-NMR were in full agreement with the material in section i.

24. Preparation of Cyclopropylidene Acetaldehyde Diethylacetal XXXI (Table 3, Entry 5):

The compound was prepared using a procedure similar to experiment 23i. Cyclopropyltriphenylphosphonium bromide[79] (10.6532 g, 0.027 mole), 19.6 mL (0.035 mole) of 1.8 M phenyllithium, and 200 mL of ether were combined as described to form the ylid which was stirred overnight. Glyoxal monoacetal (3.17 g, 0.024 mole) was added, followed 1 h later with 5.2184 g (0.0465 mole) of potassium tert-butoxide. After the usual work up and distillation (bulb to bulb) an oil was isolated, 2.95 g (78.9%). ^{1}H-NMR indicated that the acetal was contaminated with 7.1% biphenyl. bp 27-28°C (0.12 mm); IR(neat); 2950, 1670, 1475, 1390, 1160, 1140, 1070, 1020 cm.$^{-1}$

NMR(CCl_4); δ 1.1 (m, 10H), 3.5 (m, 4H), 5.0 (d, 1H, J = 6 Hz), 5.85 (m, 1H).

Hydrolysis of the acetal produced the very unstable and aggressive smelling aldehyde. The aldehyde could not be isolated without much decomposition and was not studied further.

25. Preparation of 2-Butyne-1,4-bis(triphenylphosphonium bromide) XXVII:

A 500 mL single necked round bottomed flask was charged under nitrogen with 44.5359 g (0.210 mole) of 1,4-dibromo-2-butyne and 112.3418 g (0.430 mole) of triphenylphosphine in 300 mL of dry DMF. The solution was stirred for 3 h at 80°C. The resulting precipitate, 96.5 g (62.4%) was washed well with ether and air dried. mp(methanol/water) 221-223°C.

26. Preparation of Formylmethylenetriphenylphosphorane I:[15a]

To 1500 mL of chloroform was added 100 g of 45% aqueous chloroacetaldehyde (Aldrich) and the solution was distilled until the chloroform-water azeotrope was completely removed (bp 56°C), and the solution was anhydrous. Triphenylphosphine (151.07 g, 0.576 mole) was added and the solution was refluxed for 18 h. A syrup was deposited which solidified upon cooling. The crude phosphonium salt (100.59 g, 51.2%) was recrystallized from chloroform/ethyl acetate to yield

48.18 g of the salt; mp 207-208°C dec., (lit.[15a] 212-213°C dec.).

The stabilized phosphorane was obtained by treatment of an aqueous solution of the salt with 10% sodium hydroxide; mp(acetone) 183-185°C dec., (lit.[15a] 187-188°C dec.).

The ylid also could be obtained directly by reaction of a stirred suspension of 7.5383 g (0.0211 mole) of methyltriphenylphosphonium bromide in 150 mL of dry ether under nitrogen with 10 mL (0.0245 mole) of 2.45 M n-butyllithium. The ylid was stirred for 1 h and then added to a rapidly stirred ice cold solution of 2.2086 g (0.029 mole) of ethyl formate in 100 mL of ether. The suspension was extracted with 10% hydrochloric acid. The aqueous phase was then made basic with 10% sodium hydroxide and then extracted with benzene (2x200 mL). The benzene was washed with water, dried (K_2CO_3), and concentrated in vacuo to afford 3.03 g (42.4%) of the phosphorane which was light tan in color; mp(acetone) 183-185°C dec., (lit.[15a] mp 186-187°C dec.).

27. Preparation of 4,4-Diethoxy-2-butenal XXXV (Table 4, Entry 5).[33b, 68]

A 100 mL single necked round bottomed flask equipped with magnetic stirring bar, reflux condenser and nitrogen inlet was charged with 3.6066 g (0.0106 mole) of formylmethylenetriphenylphosphorane I, 1.3886 g (0.0105 mole) of glyoxal monoacetal and 50 mL of dry toluene. The mixture was refluxed

for 16 h. The suspension was cooled, the solids were filtered, and volatiles were removed under vacuum. The residue was distilled to afford 1.1206 g (67.5%, unoptimized) of the desired acetal; bp 43-48°C (0.05 mm), (lit.[33b, 68] 45-50°C (0.15 mm)); IR(CCl_4); 2990, 2942, 2887, 2820, 2728, 1694, 1660, 1542, 1477, 1437, 1100, 1042, 990 $cm.^{-1}$
NMR(CCl_4); δ 1.22 (t, 6H, J = 7 Hz), 3.7 (m, 4H), 5.34 (d, 1H, J = 3.5 Hz), 6.43 (dd, $1H_a$, J = 16, 7 Hz), 6.95 (dd, $1H_b$, J = 16, 3.5 Hz), 9.5 (d, 1H, J = 7 Hz).

28. Preparation of 6,6-Diethoxy-(2E, 4E)-2,4-hexadienal XXXVI (Table 4, Entry 6):

The compound was prepared using a procedure similar to experiment 27. A solution of 4.05 g (0.0119 mole, 2.34 equivalents) of formylmethylenetriphenylphosphorane I and 0.6693 g (0.0051 mole) of XV in 50 mL of dry toluene was refluxed for 48 h. Work up as before and bulb to bulb distillation afforded 0.4912 g (51.8%, unoptimized) of the desired acetal as a yellow oil; IR(neat); 2980, 2930, 2720, 1680, 1635, 1600, 1470, 1440, 1140, 1100, 1060, 950 $cm.^{-1}$
NMR(CCl_4); δ 1.18 (t, 6H, J = 7 Hz), 3.58 (m, 4H), 5.07 (d, 1H, J = 3.5 Hz), 5.92-7.32 (m, 4H), 9.54 (d, 1H, J = 7 Hz).

29. Preparation of (2E, 4E, 6E)-2,4,6-Octatrienedial Through 2,4,6-Octatrienedial Diethylacetal XXXVII (Table 4, Entry 7):[69, 70]

The compound was prepared using a procedure similar to experiment 27 except that p-xylene was the solvent. A mixture of 4.6590 g (0.0137 mole, 3.28 equivalents) of I and 0.5518 g (0.0042 mole) of XV in 60 mL of dry p-xylene was heated at 140°C for 72 h. The suspension was diluted with petroleum ether and solids were removed by filtration. Volatiles were removed in vacuo and the residue was preabsorbed on basic alumina III and chromatographed on basic alumina II. After elution with (3:1) petroleum ether/ether, 0.3006 g (34.2%, unoptimized) of the desired acetal was isolated.

IR(CCl_4); 3020, 2970, 2870, 2800, 2710, 1690, 1620, 1600, 1550, 1440, 1125, 1115, 1060, 1020, 992 $cm.^{-1}$

NMR(CCl_4); δ 1.18 (t, 6H, J = 7 Hz), 3.53 (m, 4H), 4.95 (d, 1H, J = 3 Hz), 5.9-7.35 (m, 6H), 9.57 (d, 1H, J = 7 Hz).

The acetal (0.30 g, 0.0014 mole) was hydrolyzed in the usual way to yield after chromatography on silica gel (elution with (3:1) petroleum ether/ether) 0.1602 g (82.5%) of the desired dial.[69, 70] The gas chromatogram showed one unidentified impurity; IR($CHCl_3$); 3130, 3000, 2710, 1670, 1620, 1430, 1115, 1010, 990 $cm.^{-1}$

NMR(CCl_4); δ 6.0-7.5 (m, 6H), 9.7 (dd, 2H, J = 7, 1.5 Hz).

MS(70 eV); m/e 136(M^+), 134, 107, 106, 105, 81, 79, 78, 77(base).

30. Preparation of 1,1-Diethoxy-3,3-dicarbomethoxy-2-propene LIII:

The procedure of Lehnert was followed.[49] A 250 mL three necked round bottomed flask fitted with magnetic stirring bar, reflux condenser with nitrogen inlet, KOH drying tube, and 50 mL dropping funnel was charged with 100 mL of dry THF. To the rapidly stirred THF at 0-5°C was added 9.3429 g (0.0492 mole) of titanium tetrachloride in 15 mL of dry CCl_4. A yellow precipitate formed immediately, then 3.3214 g (0.0251 mole) of XV in 6 mL of THF was added dropwise, followed by 3.5369 g (0.0267 mole) of dimethyl malonate LIV in 13 mL of THF all at 0-5°C. Finally 8.1007 g (0.1025 mole) of dry pyridine in 22 mL of dry THF was added slowly over a 2 h period at 0-5°C to the rapidly stirred suspension. The reaction mixture was stirred at ambient temperature for ca. 21 h. Solids were removed by filtration and the filter cake was thoroughly washed with ether. The organic layer was washed with water (2x200 mL), the aqueous phase was extracted with 50 mL of fresh ether, and the combined ether extracts were washed with 150 mL of brine. The ether was dried (K_2CO_3) and concentrated *in vacuo*. Distillation of the residue afforded the desired acetal, 3.5726 g (58.1%, unoptimized). bp 119-125°C (1.3 mm). IR was not taken. NMR(CCl_4); δ 1.18 (t, 6H, J = 6 Hz), 3.48 (m, 4H), 3.57 (s, 6H), 5.12 (d, 1H, J = 5 Hz), 6.62 (d, 1H, J = 5 Hz).

31. Preparation of 3-Ethoxy-5,5-dimethyl-2-cyclohexenone XLIII (Scheme I):[45a, b]

A 1 L round bottomed flask fitted with a Dean-Stark trap was charged with 50.30 g (0.3588 mole) of 5,5-dimethyl-1,3-cyclohexanedione XLII (Fluka Chem. Co.), 50.2 g (1.09 mole) of ethanol, 1.5 g p-toluenesulphonic acid, and 500 mL of benzene. The contents were heated at 100°C for 16 h. The benzene was washed with $NaHCO_3$, water, and dried ($MgSO_4$). The benzene was removed in vacuo and the remaining oil was distilled to afford 56.59 g (93.9%) of the desired enol ether; bp 74-75°C (0.1 mm), (lit.[45a] 97-105°C (2 mm)). The compound crystallized on standing; mp 58-59°C, (lit.[45b] mp 57-58°C). NMR(CCl_4); δ 1.0 (s, 6H), 1.29 (t, 3H, J = 7 Hz), 2.0 (s, 2H), 2.17 (s, 2H), 3.75 (q, 2H, J = 7 Hz), 5.05 (s, 1H).

32. Preparation of 5,5-Dimethyl-2-cyclohexenone XLV (Scheme I):[45a, b]

A 1 L three necked round bottomed flask equipped with a mechanical stirrer, reflux condenser with KOH drying tube, nitrogen inlet and 500 mL dropping funnel was charged with ca. 400 mL of dry ether and 5.80 g (0.153 mole) of lithium aluminum hydride at 0-5°C. Enol ether XLIII (87.86 g, 0.52 mole) in ca. 300 mL of ether was added over ca. 1 h at 0-5°C with vigorous stirring. The flask was stirred at ambient temperature for 2 h and then cooled to 0-5°C. Ten mL of water

added, followed by 10% sulfuric acid (100 mL) which dissolved all suspended solids. The ether was washed with $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated *in vacuo*. Distillation of the remaining oil furnished 56.98 g (94.55% based on recovered starting material) of the desired enone; bp 40-47°C (1 mm), (lit.[45a] bp 40-48°C (1.6 mm)).
IR(neat); 3043, 2968, 2878, 2828, 1676, 1618, 1467, 1386 $cm.^{-1}$
NMR(CCl_4); δ 1.05 (s, 6H), 2.1-2.35 (m 4H), 6.0 (dt, 1H, J = 10, 2 Hz), 6.8 (dt, 1H, J = 10, 4 Hz).

Enol ether XLIII (6.0960 g) was recovered by further distillation.

33. Preparation of 5,5-Dimethylcyclohexenol XLVI (Scheme I):[45a]

i. By reduction with lithium aluminum hydride;

The compound was obtained using a procedure similar to experiment 32 except that ammonium chloride solution was used to quench the reaction after water was added. XLV (56.98 g, 0.459 mole) in 300 mL of ether was added to 5.05 g (0.135 mole) of lithium aluminum hydride in 300 mL of ether as previously described. After the usual work up and distillation, 53.2135 g (91.9%) of the desired allylic alcohol was isolated. Gas chromatographic analysis indicated the compound was contaminated with 9.9% starting enone XLV; bp 50-51°C (1.3 mm), (lit.[45a] 86-88°C (17 mm)).
IR(CCl_4); 3350, 3040, 2965, 2935, 2915, 2880, 2841, 1680, 1548,

1462, 1365, 1240, 1035 $cm.^{-1}$

NMR(CCl_4); δ 0.89 (br s, 3H), 0.92 (s, 3H), 1.15-1.9 (m, 4H), 3.9 (s, 1H, exchanges with D_2O), 4.15 (m, 1H), 5.42 (br s, 2H).

ii. By reduction with 9-borabicyclo(3.3.1)nonane;

The procedure of Brown and Krishnamurthy was followed.[46] A 500 mL three necked round bottomed flask equipped with a serum cap, reflux condenser, KOH drying tube, nitrogen inlet and 250 mL dropping funnel was charged with 100 mL of dry THF and 12.6693 g (0.102 mole) of XLV. To the rapidly stirred solution was added 225 mL (0.1125 mole) of 0.5 M 9-BBN over ca. 1 h at 0-5°C. Stirring was continued for 2 h at 0-5°C and for 2 h at ambient temperature. An explosion screen was placed around the flask and 50 mL of 3N NaOH was added, followed by 40 mL of 30% hydrogen peroxide all at 0-5°C. The reaction was stirred at 53°C overnight. The organic phase was washed with water (3x30 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Distillation of the residue afforded 12.0133 g (93.5%) of the desired allylic alcohol XLVI. Gas chromatographic analysis indicated the alcohol was at least 97.2% pure, contaminated with less than 1% of the enone XLV. Spectral properties were identical with section i.

34. Preparation of 5,5-Dimethylbromocyclohex-2-ene XLVII (Scheme I):

The procedure of Shenoy, Schaefer, and Higgins was used.[47]

A 500 mL three necked round bottomed flask equipped with a mechanical stirrer, reflux condenser with drying tube, and a 250 mL dropping funnel was charged with 81.33 g (0.310 mole) of triphenylphosphine and ca. 300 mL dry acetonitrile. Bromine (48.3 g, 0.32 mole) was added followed by 37.8084 g (0.270 mole) of 90% pure XLVI in 50 mL of acetonitrile. The reaction was mildly exothermic and was moderated with a bath of cold water. At the end of the addition any solids remaining in the reaction flask were dissolved by heating the flask with a heat gun. After cooling the reaction contents were poured onto 600 mL of hexane. Triphenylphosphine oxide was filtered off. The organic layer was washed with water (2x300 mL) and brine (2x200 mL), dried ($MgSO_4$), and concentrated in vacuo. The resulting liquid was distilled to afford 38.4415 g (75.4%) of the desired bromide. TLC and GC indicated the bromide was pure; bp 40-43°C (0.1 mm).
IR(neat); 3040, 2960, 2908, 2877, 2838, 1640, 1462, 1368, 1280, 1120, 722 $cm.^{-1}$
NMR(CCl_4); δ 0.91 (s, 3H), 1.03 (s, 3H), 1.7-2.1 (m, 4H), 4.7 (m, 1H), 5.77 (m, 2H).

35. Preparation of 5,5-Dimethyl-2-cyclohexenyltriphenylphosphonium Bromide XLVIII (Scheme I):

A 500 mL single necked round bottomed flask equipped with

a reflux condenser and drying tube with nitrogen inlet was charged with 37.9140 g (0.2007 mole) of XLVII and 55.07 g (0.21 mole) of triphenylphosphine. The flask was heated at 100-110°C for 16 h. Upon slow cooling a glassy, but crystalline phosphonium salt was obtained, 81.2256 g (89.7%); mp(crude) 86-93°C. This material resisted all attempts at recrystallization and was used without further purification.

In order to obtain an analytical sample, the following procedure was used. About 25 g of the syrupy phosphonium salt XLVIII was taken up in aqueous potassium iodide (ca. 150 mL) and after standing a number of days a precipitate was deposited which was recrystallized from methanol, 3.6852 g; mp 158-163°C (dec.).

Analysis: Found; C, 62.39, H, 5.50, P, 6.35, I, 25.67.
Calculated; C, 62.66, H, 5.62, P, 6.22, I, 25.48.

A crystalline tetrafluoroborate could also be obtained by an analogous procedure with the iodide or bromide from a solution of sodium tetrafluoroborate / fluoroboric acid.

36. Preparation of 5,5-Dimethylcyclohex-2-enylidene Acetaldehyde Diethylacetal XLIX (Scheme I):

A 250 mL Schlenk tube equipped with a magnetic stirring bar was charged under nitrogen with 3.3645 g (0.0073 mole) of crude 5,5-dimethyl-2-cyclohexenyltriphenylphosphonium tetrafluoroborate. The suspension was cooled to 0°C and 4 mL (0.096

mole) of 2.4 M n-butyllithium was added dropwise to the rapidly stirred suspension in 150 mL of dry hexane. The ylid was stirred at ambient temperature for 2 h, and then refluxed for 1 h. The dark red ylid was cooled to ambient temperature and 2.0443 g (0.0155 mole) of XV in 10 mL of dry hexane was added. The ylid was decolorized to a bright yellow, and stirring was continued overnight. Solids were filtered, the reaction mixture was poured onto cold dilute KOH solution, and was worked up in the usual way. Distillation (bulb to bulb) of the remaining oil afforded 0.255 g (15.6%) of the desired acetal XLIX. There was considerable decomposition during this distillation. IR(CCl_4); 3025, 2960, 2930, 2875, 1665, 1600, 1200, 1100, 1050 $cm.^{-1}$

NMR(CCl_4); δ 0.98 (s, 6H), 1.0-1.6 (m, 8H), 2.05 (d, 2H, J = 5 Hz), 3.68 (m, 4H), 5.15-6.62 (m, 4H).

When the crude crystalline bromide XLVIII was used in this reaction, the ^{1}H-NMR of the product showed different line shapes and the integration for the vinylic protons was incorrect. The acetal XLIX may be very sensitive to distillation. However, this material was used in subsequent experiments.

The diene acetal XLIX could be hydrolyzed in the usual way to afford diene aldehyde LII as a mixture of isomers after bulb to bulb distillation.

IR(CCl_4); 2970, 2940, 2880, 1672, 1620, 1540, 1250 $cm.^{-1}$

NMR(CCl_4); δ 1.04 (s, 6H), 1.5 (m, 4H), 5.47 (m, 1H), 5.82 (s, 2H), 9.90 (d, ca.0.6H, J = 7.5 Hz), 9.95 (d, 0.4H, J = 7.5 Hz). There were unidentified signals at δ 2.4 and 2.8 ppm.
MS(70 eV); 150 (M^+), 135, 117, 115, 108, 107, 105, 91 (base), 81, 77, 65, 55.

37. Attempted Synthesis of (E) and (Z)-3,3-Dimethylcyclohexylidene Acetaldehyde XL and XLI (Scheme I):

The diene acetal XLIX (1.0924 g, 0.0055 mole) was hydrogenated over 10% palladium on charcoal in absolute ethanol by bubbling hydrogen through the mixture for 18 h at ambient temperature. The catalyst was filtered, dilute HCl was added at 0-5°C, and stirring was continued for 2 h. The reaction was worked up in the usual way and afforded after distillation (bulb to bulb) an α,β-unsaturated aldehyde, 0.6411 g (76.7%). Although there were changes in the ^{1}H-NMR spectrum consistent with the structures XL and XLI, the mass spectrum of the product was identical with LII (experiment 36). This means that acetal XLIX was unreactive to hydrogenation using the conditions described.

38. Preparation of 3,3-Dimethylbromocyclohexane LI:[48]

A 500 mL three necked round bottomed flask equipped with a mechanical stirrer, condenser, and gas inlet was charged with 20.2699 g (0.1584 mole) of 3,3-dimethylcyclohexanol L (98% pure). Hydrogen bromide gas was passed through L for 0.5 h at 5°C, for 0.25 h at 100°C and for 1 h at 130°C. The reaction product was washed with concentrated sulfuric acid and then diluted with ethyl acetate. The organic phase was washed with 50% methanol/ammonium hydroxide until basic and finally with water. The organic phase was dried ($MgSO_4$), concentrated in vacuo and the residue was distilled to afford LI, 22.0182 g (74.5%). The compound was pure by TLC and GC analysis; bp 39-40°C (0.5 mm), (lit.[48] bp 63-63.5°C).

NMR(CCl_4); δ 0.92 (s, 3H), 0.97 (s, 3H), 1.2-2.1 (m, 8H), 4.1 (m, 1H).

IR was not taken.

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II

AN APPROACH TO 13-METHYLPHENALENE-A BRIDGED [12]ANNULENE

Chapter One

Introduction

A. [12]Annulenes-Theoretical And Historical Background.

The term annulene has been applied to that series of monocyclic polyolefins, $C_{2\underline{m}}H_{2\underline{m}}$ ($\underline{m}$=2,3,4....), containing a complete contiguous set of double bonds.[1,2] All the C-atoms are sp^2-hybridized. Benzene, [6]annulene, is the most common member of this class of compound. Much interest has been generated in the higher homologs.

Benzene with six π-electrons does not behave as a typical reactive polyolefin. E. Hückel was the first to recognize this extra stability and postulate a theory to explain it.[3] Hückel's rule stated in an extended and more modern version is as follows:

> "For polyenes with 4n+2 C-atoms in the path of conjugation, the π-electron energies of the annulenes, $C_{(4n+2)}H_{(4n+2)}$, will be lower (more stable) than those of the linear polyenes, $C_{(4n+2)}H_{(4n+4)}$, whereas the reverse is true for the annulenes, $C_{4n}H_{4n}$, which have π-electron energies greater than those of the corresponding linear polyenes, $C_{4n}H_{(4n+2)}$ (less stable)."[4]

Hückel's rule as originally formulated only mentioned the extra stability of systems with 4n+2 π-electrons. Systems with 4n π-electrons are now known to be less stable than the analogous 4n+2 π-electron system and this observation has been incorporated into the Hückel theory.

According to the simple Hückel theory the annulenes, if planar, should all have their total π-energy less than $\underline{m}$ times that of the ethylene molecule. The resulting stability

gain is defined as the delocalization energy (DE),[2] (eq 1)

$$DE = -(E_{\pi \text{ total}} - \underline{m}E_{\pi \text{ ethylene}}) \qquad (1)$$

where $E_{\pi \text{ total}}$ is the total π-energy and $E_{\pi \text{ ethylene}}$ is the π-energy in the ethylene molecule. According to this simple Hückel approach the DE should increase as $\underline{m}$ increases; however, when expressed per C-atom (DE/2$\underline{m}$), this stabilization energy should be greater for the annulenes with $2\underline{m}=4n+2$ π-electrons ($\underline{m}$ odd) than for the annulenes with $\underline{m}=4n$ π-electrons ($\underline{m}$ even).[2] This principle is shown in Figure 1.

Although the simple Hückel theory predicts extra stability for 4n systems, this is not verified by experimental fact, (<u>vide infra</u>) (Figure 1). Annulenes with 4n π-electrons are less stable chemically than annulenes with 4n+2 π-electrons. More elaborate π-energy calculations by Dewar and Gleicher have shown that the resonance energy (RE) (defined as the difference between the calculated heat of formation of a given molecule and heat of formation calculated for a single classical structure using empirical bond energies[5]) for 4n+2 annulenes is positive and the RE for 4n annulenes is negative[5] (Figure 1).

A planar molecule possessing cyclic delocalization is considered <u>aromatic</u> if its RE is greater than zero. (Figure 1). Figure 1 shows that only 4n+2 annulenes possess positive RE, while the 4n annulenes possess negative or zero RE. Therefore, these 4n systems are termed <u>antiaromatic</u>[6], (Figure 1).

Unfortunately, the determination of aromaticity or anti-

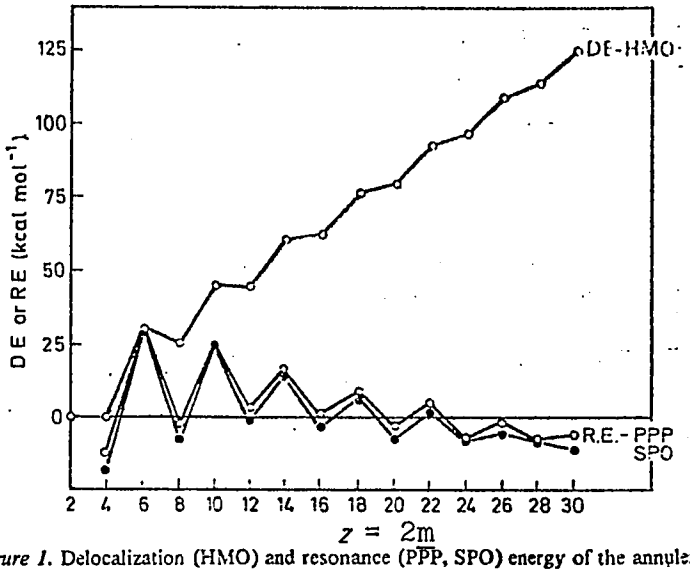


Figure 1. Delocalization (HMO) and resonance (PPP, SPO) energy of the annulenes. [5]

(PPP=Pariser-Parr-Pople Method[5], SPO=Split p-Orbital Method[5])

aromaticity can not be solely based on the number of π-electrons, and the resonance energy, a very difficult to obtain experimental quantity. Other factors which are important include the strain energy associated with the molecule, especially when considered in its planar conformation, and the degree of bond alternation.

Experimentally, molecules of the 4n+2 type like benzene were observed to possess unusually high diamagnetism when placed in an external magnetic field perpendicular to the plane of the molecule. Pauling developed a semi-classical theory to explain the diamagnetic anisotropy in some aromatic molecules. The impression of an external magnetic field causes a flow of the π-electrons around the ring.[7]

Using a quantum mechanical treatment and the earlier observations of Hückel and Pauling, London, in 1937, developed a theory to explain the high diamagnetism in 4n+2 systems

which gave good correlation with experimental observation.[8] In qualitative terms London's theory concluded that for molecules possessing $4n+2$ π-electrons in a planar cyclic conjugated array, a <u>negative</u> contribution to the diamagnetic susceptibility was made. Jackman and Elvidge used the term diamagnetic ring current to explain this phenomena.[9] A consequence of a diamagnetic ring current is that there is considerable deshielding in the molecular plane outside the ring, and even larger shielding inside or above the molecular plane, (Figure 2).

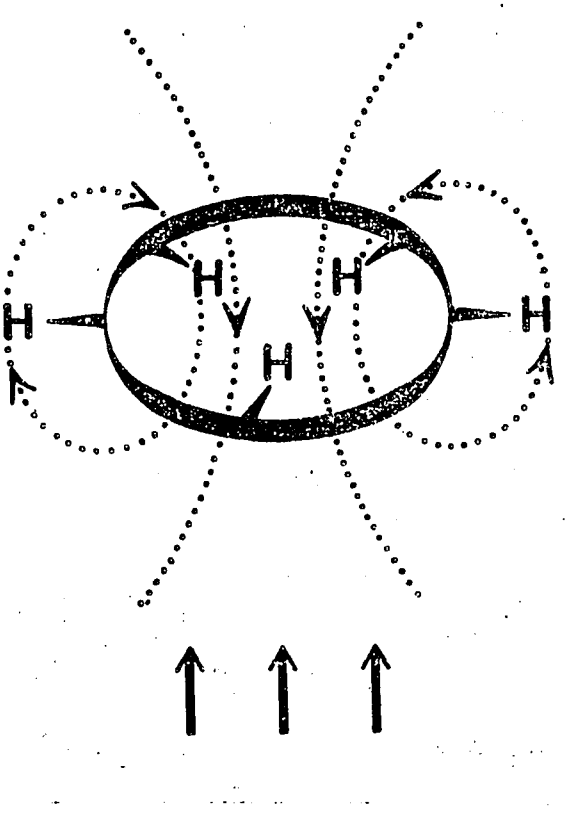


Figure 2. Diagram of Magnetic Field Associated with a Ring Current in a Monocyclic System.[4b]

In 1951 Berthier, Mayot, and Pullman showed that application of the London theory to certain hydrocarbons of the 4n type led to a positive contribution to the diamagnetic susceptibility.[10] Thus the impression of an external magnetic field on 4n systems results in the formation of a paramagnetic ring current. The previously stated shielding effects are reversed in a paramagnetic ring current. Thus there is considerable shielding in the molecular plane and even more deshielding inside or above the molecular plane.

In 1966 Pople and Untch further examined induced ring currents and made the following observations:[11]

1. For all degrees of bond alternation the London theory always predicts a negative contribution to the diamagnetic susceptibility (diamagnetic ring current) when there are 4n+2 π-electrons. When there are 4n π-electrons the theory predicts a positive contribution to the diamagnetic susceptibility (paramagnetic ring current).

2. For all sizes of rings the degree of the induced ring current effect is quenched with bond alternation. Larger rings are affected more by a given amount of bond alternation. Qualitatively, the induced ring current in 4n systems is quenched more by a given amount of bond alternation than in 4n+2 systems.

3. For 4n systems the London theory predicts infinite paramagnetism when there is no bond alternation. However, in practice all 4n systems show some bond alternation and thus

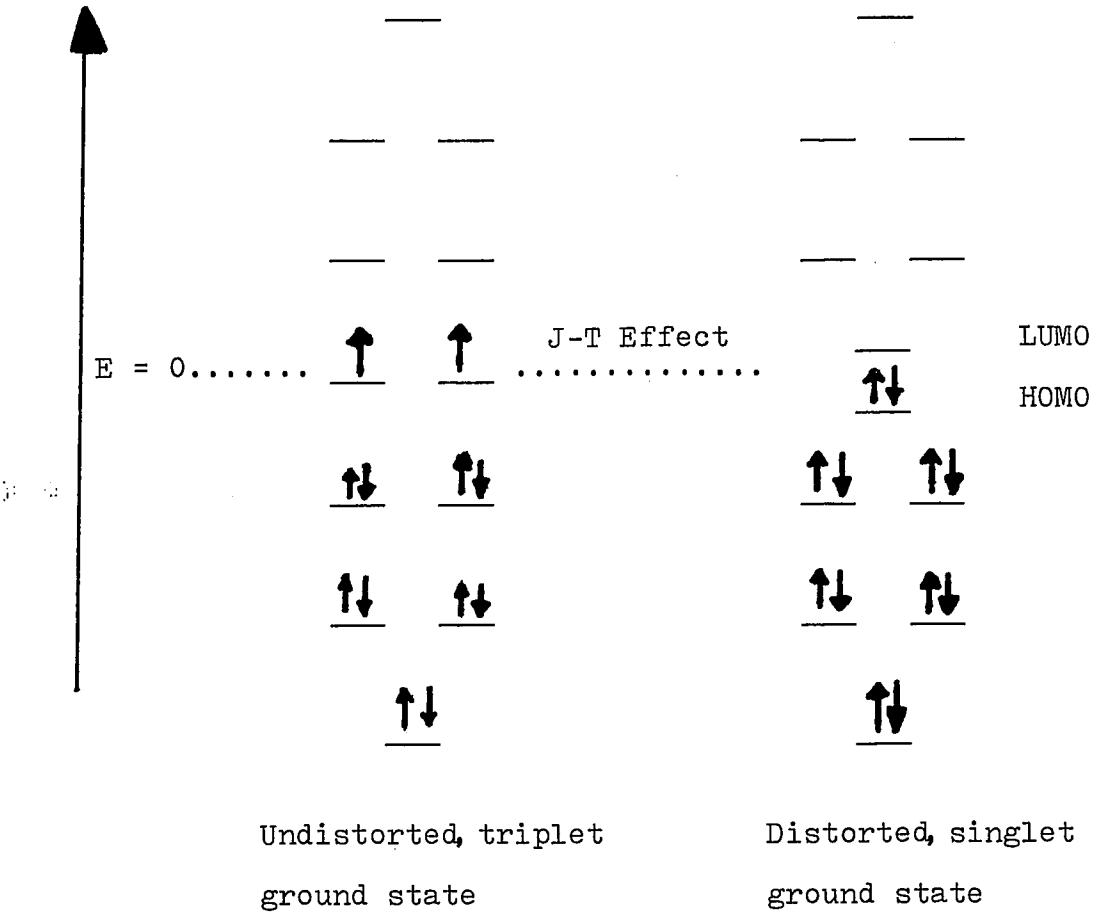


Figure 3. The Jahn-Teller Effect On The Molecular Orbitals Of A Generalized [12]Annulene.

converge to zero resonance energy, (Figure 1). At that point both series should behave as typical reactive polyolefins.

the previously stated degeneracy is removed and the paramagnetic effect takes on a finite value.

Point 3 is very important. The London theory predicts infinite paramagnetism when there is no bond alternation, but in reality all 4n systems exhibit some bond alternation. In 4n systems when there is no bond alternation the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) are degenerate, (Figure 3). This degeneracy leads to infinite paramagnetism. This degeneracy in the ground state is removed by the process of bond alternation. The ground state is now in a non-degenerate singlet state, (Figure 3). This is an example of the Jahn-Teller effect.[2] As Figure 3 shows once the ground state of a 4n system is no longer degenerate, a small HOMO-LUMO gap is created. This small energy gap may account for the relative instability of 4n systems because the energy required to raise a ground state electron to an excited state (the LUMO) is small. In addition, since the ground state is now non-degenerate the paramagnetism in 4n systems becomes finite.

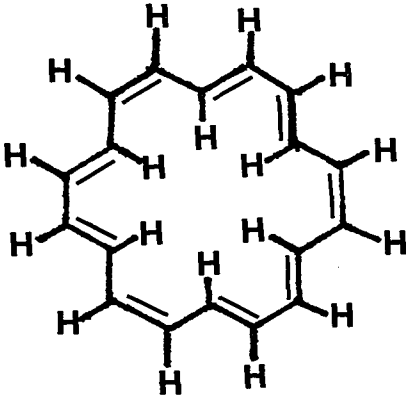
The Jahn-Teller distortion becomes very important for small 4n annulenes and is still important in larger 4n+2 annulenes. The calculations of Dewar and Gleicher[5] predict that at a ring size of 26 C-atoms bond alternation begins for 4n+2 π-systems. Consequently, [26]annulene is predicted to be non-aromatic (RE=0), (Figure 1).

The previously stated shielding effects for diatropic (4n+2 systems) and paratropic (4n systems) molecules have been measured most accurately by ^{1}H-NMR spectroscopy. Figure 4 shows some examples of 4n+2 systems that illustrate some of these shielding effects.

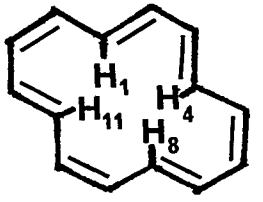
[18]Annulene I[12a] shows a temperature dependent ^{1}H-NMR spectrum. At -60°C the ^{1}H-NMR shows two signals, one set of six protons at δ -4.22[12b] and the other set of 12 protons at δ9.25. The structure as written in Figure 4 has been verified by an X-ray analysis.[13] The six inner protons are shielded and the 12 outer protons are deshielded in complete agreement with a diamagnetic ring current.

[14]Annulene II[14] exists in two major conformations. One conformation has H_1 and H_4 above H_8 and H_{11}, and the other has H_1 and H_8 above H_4 and H_{11}. The X-ray analysis supports this conclusion.[15] The temperature dependent ^{1}H-NMR spectrum at -60°C shows two sets of signals. The four internal protons resonate at δ 0.0, while the ten external protons resonate at δ 7.6. These results are fully consistent with a diamagnetic ring current.

The remaining examples in Figure 4 illustrate the use of some bridging groups in diatropic molecules. These bridging groups add rigidity to the illustrated molecules. The methylene protons in [8]paracyclophane III[16] resonate at δ 0.6, a clear manifestation of the diamagnetic ring current. 1,6-Methano-[10]annulene IV[17] shows a resonance for the



I



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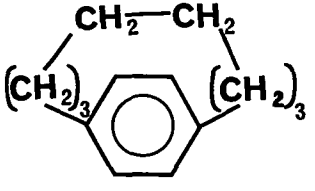

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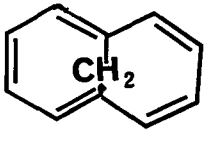

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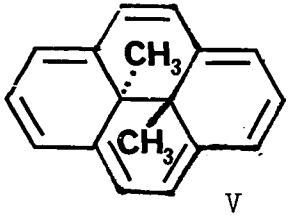
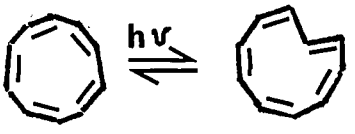


V

Figure 4. Some Selected 4n+2 π-Electron Systems.

bridging methylene protons at δ-0.5. The bridging group not only adds rigidity to the system, but also adds stability to the system. 1,6-Methano-[10]annulene can be contrasted with the unbridged [10]annulene VI, synthesized by Masamune and co-workers.[18] VI is a very unstable molecule. It behaves as a reactive polyolefin and can be only isolated at low temperature. In addition, VI shows no evidence of a diamagnetic ring current. The molecule can not assume a planar conformation because of strain factors, (eq 2).

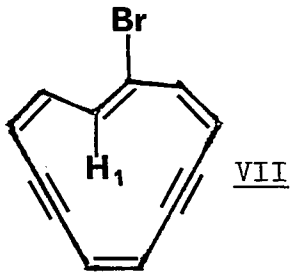


VI (2)

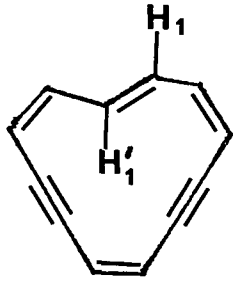
Another example of a bridged diatropic molecule is trans-15, 16-dimethyldihydropyrene V.[19] The methyl groups are within the cavity of the molecule and show a ^{1}H-NMR signal at δ-4.25

Clearly, ^{1}H-NMR can accurately determine the shielding effects in diatropic molecules. The shielding effects in paratropic molecules can also be measured accurately with ^{1}H-NMR. Figure 5 illustrates some selected 4n systems.

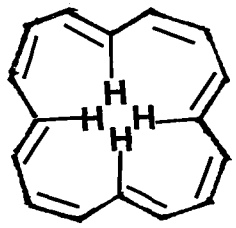
One of the first experimental observations of a paramagnetic ring current effect was in 5-bromo-1,9-didehydro-[12]annulene VII and 1,5-didehydro-[12]annulene VIII.[20] The internal



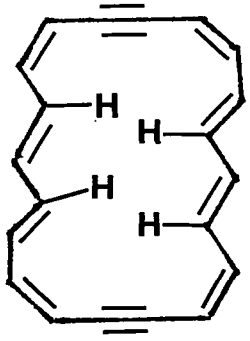
VII



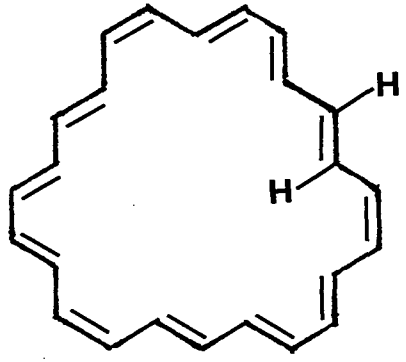
VIII



IX



X



XI

Figure 5. Some Selected 4n π-Electron Systems.

proton (H_1) in VII resonates at δ 16.4 and the internal proton (H_1') in VIII resonates at ca. δ 17. The external protons in VII resonate at δ 4.3-5.4 and the external protons in VIII resonate at δ 4.8-5.8. This data is in complete agreement with a paramagnetic ring current.

[16]Annulene IX[21] shows a temperature dependent ^{1}H-NMR spectrum. At -120°C the four internal protons resonate at δ 10.32 (triplet) and the external protons resonate at δ 5.2 (multiplet). The torsional strain angle in [16]annulene is only approximately 20°. This means the four internal protons do not suffer a severe steric interaction when the molecule assumes a planar conformation.

1,11-Didehydro-[20]annulene X, synthesized by the Sondheimer group,[22] shows typical properties of a 4n system. The internal protons resonate (-80°C) at δ 11.6 (2H) and 10.45 (2H). The external protons show signals at δ 5.17 and 5.60.

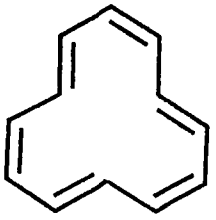
The final example in Figure 5 is [24]annulene XI, synthesized by Sondheimer and Calder.[23] This molecule also exhibits a temperature dependent ^{1}H-NMR spectrum. At -80°C the internal protons resonate at δ 11.2-12.9, while the external protons resonate at δ 4.73.

It is interesting to note that as the ring size increasess from IX through XI the internal protons are deshielded by approximately 2.6 ppm. This may mean that the larger [24]-annulene is sterically less crowded than IX or X and that XI can assume a more favorable planar geometry, thus maxi-

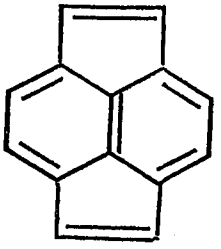
mizing the paramagnetic ring current. The external protons remain relatively insensitive to increasing ring size in going from IX to XI. These results are in complete agreement with ring current theory. The theory predicts that the degree of deshielding inside or above the ring of a 4n system will be greater than the degree of shielding outside the ring.[11]

The examples in Figure 5 clearly establish the presence of a paramagnetic ring current in unbridged 4n systems. Considerable effort was expended to obtain smaller 4n annulenes, especially with n=3.

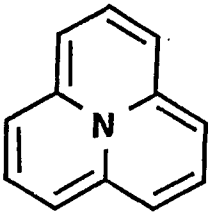
The parent annulene with n=3 is [12]annulene XII, elegantly synthesized and studied by Oth and co-workers.[24] This compound has been found to be exceptionally labile, undergoing a series of photolytic and thermal electrocyclic transannular ring closures at approximately -60°C. Its ^{1}H-NMR at -170°C exhibits two signals at δ 7.83 (3H) and δ 5.88 (9H). The signal at lower field is due to the three internal protons which experience a modest paratropic shift. This molecule has been shown to experience considerable deformation from planarity because of the non-bonding interactions of these three internal protons which cause a torsional strain angle of 50-60° for this molecule and thus its diminished paramagnetic ring current. Structure XII' illustrates this non-bonded interaction.



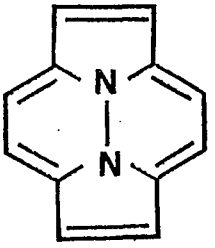
XII



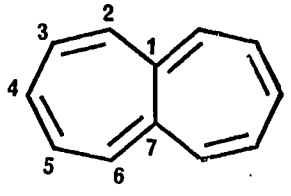
XIII



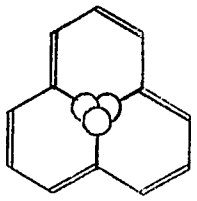
XIV



XV



XVI



XII'

The molecule is found to undergo a rapid isodynamical[25a] bond shift which makes the protons on the trans double bonds isochronous as are the protons on the cis double bonds, i.e., at -80°C there are two sets of ^{1}H-NMR signals each of six protons. One set is the protons on the trans double bonds, while the other set is the protons on the cis double bonds. The diminished paramagnetic ring current in [12]annulene XII becomes readily apparent on comparison with [16]annulene IX. As stated before the four internal protons in IX resonate at δ 10.32. Thus the perimeter in the larger IX is more planar in comparison with the smaller XII.

In extreme contrast to the very unstable [12]annulene XII the [12]annulene dianion,[26] formally a diamagnetic 14 π-electron system, is thermally stable up to 60°C. At this temperature the ^{1}H-NMR signals from the dianion disappear, probably due to a reaction with byproducts formed when XII is made. The three internal protons in the dianion now resonate at δ -4.60, a typical position for internal protons in a diatropic molecule.

Interestingly, despite the steric interactions which prevent achievement of planarity in XII, the resonance stabili-

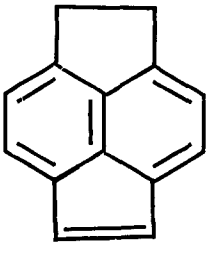
zation associated with the 14 π-electrons in the dianion of [12]annulene XII is at least 8 Kcal/mole greater than the resonance stabilization in the isoelectronic species, the neutral [14]annulene II. Simple HMO calculations indicate that the delocalization energy in the dianion of [12]annulene XII is approximately one β unit larger than in [14]annulene II.

Since the parent [12]annulene XII exhibits extreme lability, making its study quite difficult, the [12]annulene perimeter must be made more rigid. One way of doing this is by introducing various bridges preventing transannular reactions.

The use of bridging groups has been most profitably investigated by Vogel and his group in the [10]annulene field.[30] As previously discussed [10]annulene[18] was found to behave as a reactive polyolefin. In contrast to this introduction of a bridging methylene group between the 1,6 C-atoms produces a stable molecule (1,6-methano[10]annulene IV[17,27,28,29]) that shows a strong diamagnetic ring current and thus it can be classified as aromatic. Similar bridging groups have been used in the [12]annulenes.[30]

Pyracylene XIII, synthesized by Trost and co-workers,[31] formally possesses an ethylenic bridging group. Models indicate a moderate deformation from a planar geometry for this molecule. In addition this molecule is predicted to contain a strain energy of 48 Kcal/mole. The ring protons resonate at δ 6.52 (for the protons on the six membered ring)

and δ 6.01 (for the protons on the five membered ring). The 5,6-dihydro compound XIIIa shows a downfield shift of about 1 ppm for the ring vinylic protons. This indicates a weak paramagnetic ring current exists for XIII, or the shift may be due to less strain in the dihydro compound XIIIa



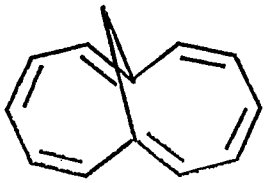
XIIIa

A bridged [12]annulene which shows an appreciable paramagnetic ring current is cycl(3.3.3)azine XIV.[32] This molecule has a nitrogen atom as the formal bridging group. The vinylic protons around the ring resonate at the exceptionally high upfield positions of δ 2.07 and 3.65. This molecule must, therefore possess a significant paramagnetic ring current. Unfortunately, with no internal protons and a hetero atom in the cavity of the molecule, an accurate assessment of this paratropic behavior is difficult to judge. One way to get information concerning the influence of the N-atom would be to study the ^{15}N-NMR of XIV and its fully and partially hydrogenated isomers.

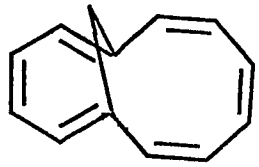
Another interesting molecule, similar to Trost's pyracylene XIII, is 8b,8c-diazacyclopent[fg]acenaphthylene XV where the

bridging group is formally a hydrazino moiety.[33] This molecule shows a modest paramagnetic ring current effect. The vinylic protons resonate at δ 5.13 (4H) and 5.22 (4H). Comparing these values with the shift positions from cycl-(3.3.3)azine XIV, it is apparent that the protons in XIV are considerably more shielded than in XV. Again it is difficult to judge the effect of the hetero atoms on the paramagnetic ring current in XV. Also XV does not possess internal protons and may be somewhat strained.

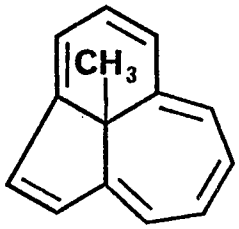
Heptalene XVI, a [12]annulene with a carbon-carbon sigma bond as the formal bridging group, is a very unstable molecule first studied by Dauben and Bertelli.[34] In its ground state this molecule is probably non-planar as shown by low temperature ^{13}C-NMR. There is a C_2 axis at -167°C. The molecule shows π-bond fixation, but also undergoes an extremely fast π-bond shift.[35,36] The ^1H-NMR signals appear at (-80°C) δ 5.02 (H_2, H_6), 5.75 (H_4), and 5.80 (H_3, H_5). These chemical shifts indicate a moderate paramagnetic ring current. The molecule can be reduced with lithium to the 14 π-dianion. This species, in contrast with heptalene XVI, is thermally very stable. The dianion has ^1H-NMR signals (-80°C) δ 5.74 (H_3, H_5), 6.25 (H_4), and 7.65 (H_2, H_6). This indicates that the net upfield shift associated with the introduction of two negative charges is more than made up for by the induced diamagnetic ring current in going from the 12 π-system to the 14 π-system.



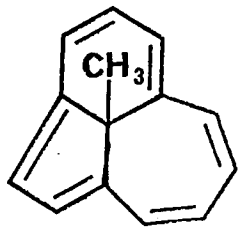
XVII



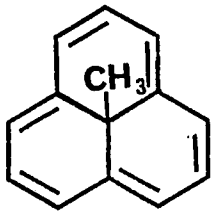
XVIII



XXI



XXII



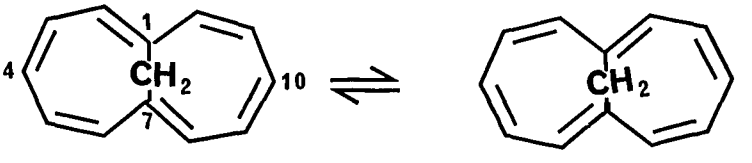
XXIII

Similar results were observed with the ^{13}C-NMR signals of the parent XVI and the dianion.[35] The large observed diamagnetic ring current points to a delocalization of the π-bonds through the dianion. These results probably mean that the dianion of heptalene XVI is planar; that is, the delocalization energy in the 14 π-system is great enough to overcome the strain energy associated with a planar geometry.

1,7-Methano[12]annulene XVII[37] can be considered the 12 π-analog of 1,6-methano[10]annulene IV.[17,30] Models indicate that XVII is only slightly puckered about the ring. In this compound the formal bridging group is a sp^3-hybridized methylene C-atom which "sits" over the face of the molecule. Therefore, this group should be a sensive marker in determining the paratropic behavior of 1,7-methano[12]annulene XVII.

The ^1H-NMR spectrum of XVII shows a temperature dependence indicating a rapid dynamic process is occurring. This process is the valence tautomerism between XVIIa and XVIIb,[37] (eq 3).

(3)



XVIIa XVIIb

The resonances appear at δ 6.16 (bridge CH_2) and 5.1-5.8 (ring protons). This is a complete reversal of the proton positions in 1,6-methano[10]annulene IV where the bridge

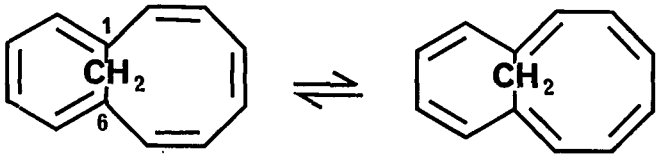
protons appear at δ -0.5 and the ring protons appear at δ 6.8-7.5. On lowering the temperature the signal from the bridge protons in XVII remains unchanged, while the signals from the ring protons broaden and change shape.[37]

The room temperature ^{13}C-NMR spectrum of XVII shows four signals for the ring carbons, indicating a rapid π-bond shift around the ring. As the temperature is lowered between -40°C and -120°C, magnetic equivalence is lost between C_2 and C_6, and between C_3 and C_5. Magnetic equivalence is not lost between C_4 and C_{10} over this temperature range. Thus at -120°C the ^{13}C-NMR spectrum shows six signals which means that the π-bond shift has essentially been frozen out.

The dianion of 1,7-methano[12]annulene XVII can be prepared with lithium or potassium in THF-d_8.[38] The dianion shows a temperature independent ^{1}H-NMR spectrum which indicates a reorganization of the bond orders around the perimeter. This can be accounted for by a delocalization of the 14 π-electrons in the 12 P_z orbitals. There is also the lesser possibility of a very rapid valence bond tautomerism. The production of an aromatic diamagnetic ring current is manifested in the position of the ^{1}H-NMR signals. The bridge protons now appear at δ -6.44 and the ring protons appear at δ 6.41-7.16. The dianion prepared at -80°C is thermally stable.

A compound related to XVII is 1,6-methano[12]annulene

XVIII which can exist in two forms, XVIIIa and XVIIIb.[39] These two forms can be in equilibrium or one form may not appear at all. The process leading from one to the other is a non-isodynamical[25b] valence bond tautomerism, (eq 4). Models indicate that XVIIIa should be more favored energetically than XVIIIb.



(4)

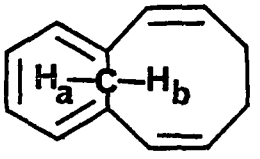
XVIIIa XVIIIb

Valence tautomer XVIIIa possesses the relatively rigid conformation XVIIIa' or XVIIIa":

XVIIIa' XVIIIa"

These conformations show considerable deviation from a planar ring geometry. The ^{1}H-NMR spectrum of XVIII shows no significant temperature dependence. The signals are located at δ 6.17 (H_3, H_4) and 5.73 (H_2, H_5) as an AA'BB' system, 5.5 (H_7 to H_{12}), and an AB system at 2.29 (H_{13a}) and 7.0 (H_{13b}) with a coupling constant of -11.5 Hz. The AA'BB' system is

consistent with a partial cycloheptatriene structure which indicates the valence tautomer XVIIIa must be the predominant, if not exclusive form. The remarkable splitting of the bridge protons must indicate that the preferred conformation is XVIIIa' which puts H_{13b} much closer to the paramagnetic ring current and consequently deshields this proton much more than H_{13a}. Although there is moderately strong deviation from planarity, the authors conclude the compound possesses a moderate paramagnetic ring current. This is apparent on comparison with 9,10-dihydro-1,6-methano[12]annulene XIX.



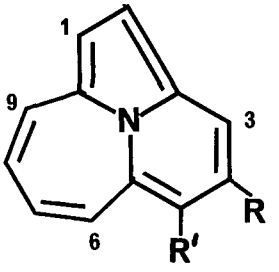
XIX

On going from XIX to XVIII the signals from the AA'BB' system are shifted 0.5 ppm upfield, while the doublets of H_{13a} and H_{13b} are shifted about 0.72 and 3.87 ppm, respectively, downfield.

The dianion of 1,6-methano[12]annulene XVIII can be prepared in a similar fashion to the 1,7-isomer.[38] The annulene protons experience a 1-2 ppm downfield shift in going to the dianion and the bridge protons experience a upfield shift, appearing at δ -5.52 and -6.08. This is completely consistent with a diatropic 14 π-electron Hückeloid system. The fact that the bridge protons now appear in almost identical shift

positions is compelling evidence that the previously distorted [12]annulene perimeter has flattened due to the increase in resonance stabilization which can compensate for the ring strain in a planar species. The ^{1}H-NMR spectrum is essentially temperature independent, indicating that the molecule in the dianion form is now delocalized. The dianion is thermally stable.

A molecule related to cycl(3.3.3)azine XIV is cycl(4.3.2)-azine XX (9b-azabenz[cd]azulene, R=R'=H).



XX

This molecule also possesses a 12 π-electron perimeter, but here the rings are annelated in a non-symmetric fashion. The synthesis of XX has been attempted, but the compound with R=R'=COOEt was obtained and could not be transformed further to XX.[40] The ^{1}H-NMR of XX (R=R'=COOEt) shows resonances at δ 4.92 (H_1), 5.02 (H_2), 6.0 (H_3), 3.97 (H_6), 3.65 (H_7), 3.36 (H_8), and 4.06 (H_9). With no internal protons in this molecule it is difficult to judge the degree and magnitude of the paratropism of this molecule.

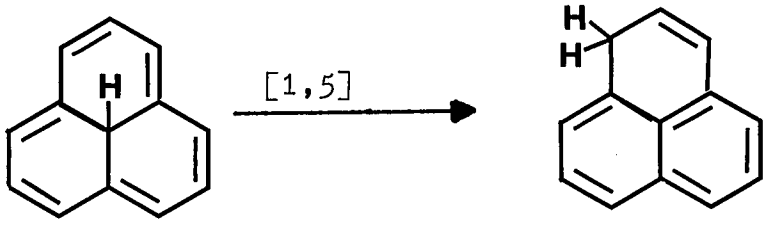
The carbocyclic analogs of cycl(4.3.2)azine XX (R=R'=H)

are the 9b-methyl-9b-hydro-1,2a,4,5a,7,9-benz[cd]azulene XXI and 9b-methyl-9b-hydro-2,3,5,6,8,9a-benz[cd]azulene XXII. These valence tautomers possess a methyl group in the internal π-cavity of the molecule, which would be good probes in analyzing the paratropism in these as yet unknown molecules. Model considerations indicate that XXI and XXII show considerable deviation from planarity because of the dissymmetric ring annelation.

The best example of a bridged [12]annulene is 13-methylphenalene XXIII,[41] a molecule that has long been sought (see Chapter 1, section B). This molecule has an sp^3-hybridized C-atom as the bridging group with a methyl group attached to this bridging carbon. Formally this represents a replacement of the three internal protons of [12]annulene XII by sigma bonds to carbon. An examination of a Dreiding model indicates that introduction of the sp^3-hybridized carbon causes very little deviation from planarity about the annulus. The internal bridging carbon "sits" at an angle of 15-20° above a mean plane formed by the ring carbons. The internal methyl group should act as a sensitive marker in studying any paratropic behavior this molecule is expected to exhibit when it is placed in an external magnetic field.

The internal methyl group in 13-methylphenalene XXIII is also expected to increase the stability of the molecule relative to the hydrogen substituted analog and to hinder

any thermally allowed [1,5]sigmatropic migration, which may be a facile process when a proton is substituted for the methyl group. This is illustrated in eq 5.



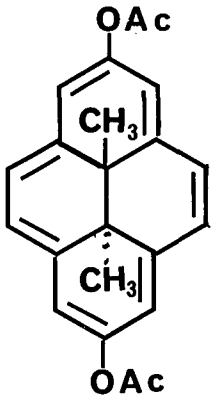
(5)

Because of the rigidity and high symmetry in XXIII it is expected that XXIII will exist as a stable crystalline material, which would make an X-ray study appropriate.

Thus as the previous discussion has shown, there are few [12]annulenes known that combine stability, rigidity, planarity of structure, and unambiguous structural features that makes determination of the presence of a paramagnetic ring current easy, and not subject to extraneous effects, such as those due to a heteroatom(s), or an extra π-system in the cavity of the ring. This should make 13-methylphenalene XXIII the ideal example of a bridged [12]annulene and consequently its synthesis and investigation should considerably advance our understanding of paratropism in $4n$ systems.

B. Previous Approaches To 13-Methylphenalene XXIII And Related Systems.

Bridged [14]annulenes which bear a striking resemblance to 13-methylphenalene XXIII are the trans and cis-15,16-dimethyldihydropyrenes V and Va respectively, elegantly synthesized by V. Boekelheide and co-workers.[42,43] The perimeter of the trans isomer is essentially planar. In fact X-ray crystallographic examination of 2,7-diacetoxy-15,16-dimethyl pyrene Vb has shown that no C-atom deviates more than 0.027 A from a mean plane.[42] In addition the bond distances in this molecule vary between 1.386 A and 1.401 A, in excellent agreement with the standard benzene bond distance of 1.397 A.[44] This molecule (Vb) has high diamagnetic susceptibility.



Vb

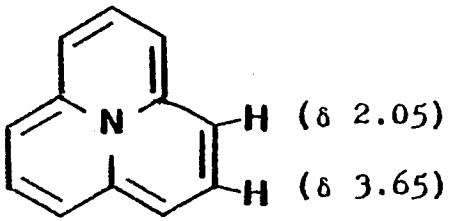
Trans-15,16-dimethyldihydropyrene V also behaves as an aromatic molecule in that it readily undergoes electrophilic

substitution reactions. In fact it is slightly more reactive than benzene. The ^{1}H-NMR signals for this molecule, (Figure 6), appear at typically upfield positions for the internal methyls (δ -4.25) and typically downfield for the ring protons (δ 7.98-8.67). This molecule is in all senses diatropic and aromatic.

The dianion of trans-15,16-dimethyldihydropyrene V can be prepared with lithium or potassium in THF-d_8. The dianion is now a 16 π-electron paramagnetic species and experiences a complete reversal of the signals in the ^{1}H-NMR. The internal methyl groups now appear at δ 21.0. This is a shift of over 25 ppm from the neutral molecule![45] The ring protons in the dianion appear at δ -3.19 to -3.96

Substitution of the internal methyl groups in V with hydrogen leads to facile oxidation to pyrene, (eq 6). This last reaction illustrates the use of the internal methyl groups as stabilizers, preventing certain side reactions from occurring.

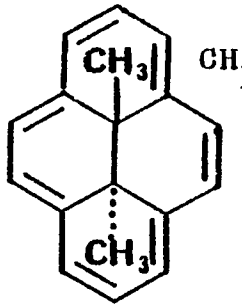
Cis-15,16-dimethyldihydropyrene Va, (Figure 6), shows analogous results except that since this molecule is more saucer shaped than the trans isomer, the internal methyls sit further away from the source of the diamagnetic ring current. Consequently, these methyl protons resonate at δ -2.06.[45a] This is about 2 ppm downfield from the position of the internal protons in the trans isomer,[46] (Figure 6).



(δ 2.05)

(δ 3.65)

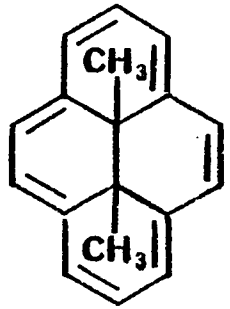
XIV



CH_3 (δ -4.25)

Ring Protons
δ7.98-8.67

V

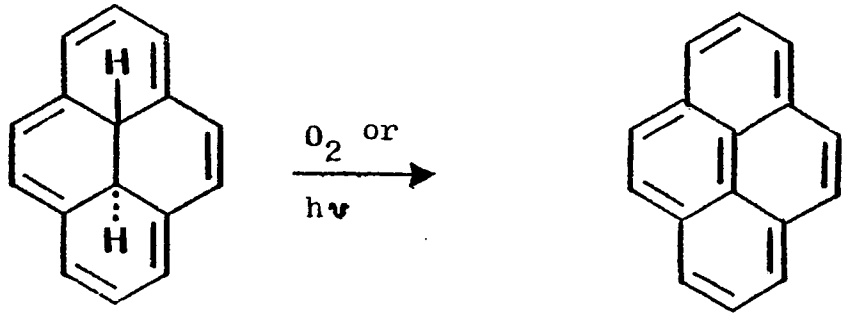


CH_3 (δ -2.06)

Ring Protons
δ7.50-8.74

Va

Figure 6. ^{1}H-NMR of Some Systems Related to 13-Methylphenalene XXIII.



(6)

The first attempts at the synthesis of 13-methylphenalene XXIII involved attempted trapping of the phenalene anion XXIV[47,48] or the phenalenium cation XXV[49,50,51] with suitable electrophilic or nucleophilic reagents, (Figure 7). The phenalenyl anion XXIV has been prepared by Boekelheide and Larrabee[47] by treatment of phenalene XXVI with phenyllithium. They trapped the anion with methyl iodide, but they did not isolate XXIII. Instead the products isolated were 4-methylphenalene XXVII and 9-methylphenalene XXVIII, (Figure 7). Significantly, no 2-methylphenalene was observed.

The anion of phenalene XXIV[48] shows ^{1}H-NMR signals at δ 5.17 (d, 6H) and 5.91 (t, 3H). As predicted from molecular orbital calculations the phenalenyl anion XXIV, the phenalenium cation XXV and the phenalenyl radical are stable.[52c,d,e] A stable phenalenium salt has been prepared by Pettit[49] and a more general method to prepare phenalenium cations has been developed by Reid and co-workers,[50] (Figure 7). Attempts at trapping the cation XXV with reagents like methyllithium did not result in the formation of 13-methylphenalene, but instead yield ring methylated products,[51] (Figure 7). The phenalenium cation XXV has also been obtained using fluorosulfonic acid and antimony pentafluoride.[52a,b]

The reason that the phenalenium cation XXV or anion XXIV do not give 13-methylphenalene XXIII can be clearly understood when one analyzes the positions of the electronic charge distribution around the ring.[52c] Figure 8 shows that

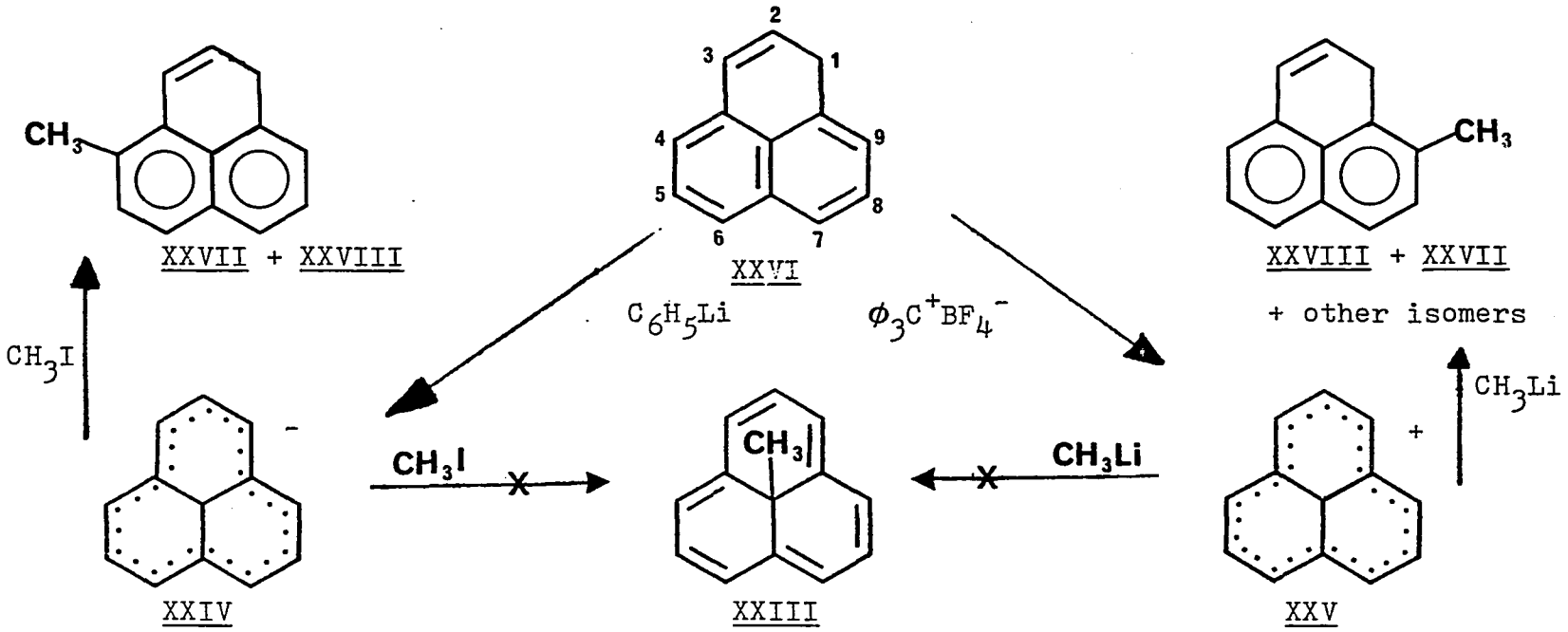
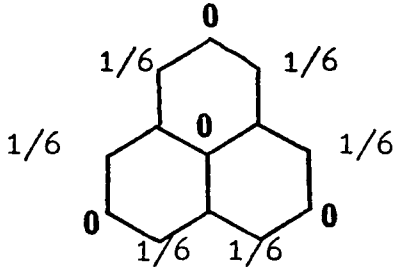


Figure 7. Some Reactions of Phenalene XXVI.



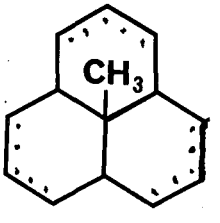
For The Cation And Anion

Figure 8. Electronic Charge Distribution in the Phenalene Anion XXIV and Cation XXV.

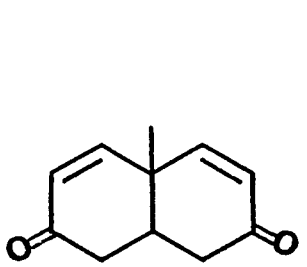
the charge is zero at the central carbon and at C_2, C_5, and C_8 thus making it impossible for an electrophilic or nucleophilic reaction to occur at these positions. With this limitation in mind the use of phenalene XXVI as a starting material for the synthesis of 13-methylphenalene XXIII becomes all but impossible.

Grohmann and Hermoso tried an approach to 13-methylphenalene XXIII which offered much promise, but no definite result is as yet forthcoming.[53] The Grohmann and Hermoso approach uses the known, but not so readily available tricyclic trione XXIX, (eq 7a).[54] This compound is available through the bis-Michael reaction of dimethyl acetone dicarboxylate on the bis-enone XXX.[54] The intermediate diester is hydrolyzed and decarboxylated to give the desired tricyclic trione XXIX, (eq 7a). This compound has the central methyl group in place and has three potential double bonds through suitable elaboration of the keto groups.

The tris-tosylhydrazone of XXIX was made *in situ* and treated with excess methyllithium. A seven component mixture was isolated. The fifth peak in the GC-MS gave a molecular ion at m/e 186 in agreement with the proposed structure XXXI.



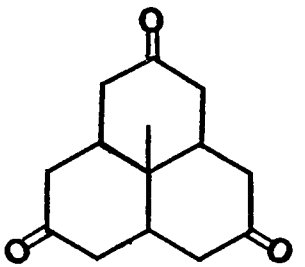
XXXI



XXX

1. $O=C(CH_2COOCH_3)_2/NaOCH_3$

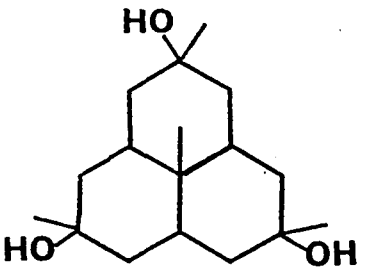
2. H_2SO_4/H_2O



XXIX

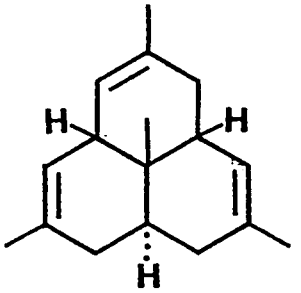
(7a)

CH_3Li



XXXII

$KHSO_4$



XXXIII

(7b)

The ^{1}H-NMR indicated a mixture of isomers for XXXI. The entire seven component mixture was allowed to react with molecular bromine and the crude bromide was dehydrobrominated with potassium tert-butoxide. After work up an oil was isolated which could not be purified for detailed analysis. The compound(s) may have decomposed on attempted chromatographic purification.

Grohmann and Noire have tried a different approach with tricyclic trione XXIX. This compound was treated with excess methyllithium. After work up by continuous extraction a high yield of the tertiary triol XXXII was obtained, (eq 7b). This compound was subjected to dehydration with potassium bisulfate. A compound was distilled whose mass spectrum was consistent with the desired tricyclic triene XXXIII, (eq 7b). No further work has been done along these lines owing to the difficulties in obtaining bis-enone XXX. A new and entirely different approach has been developed toward a synthesis of 13-methylphenalene XXIII. This approach is the subject of the next chapter.

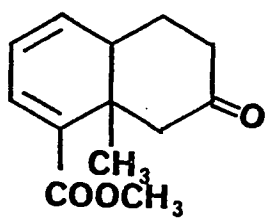
Chapter Two

Discussion

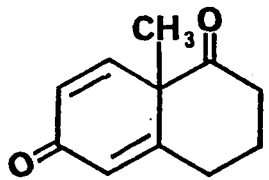
A. Synthesis of Precursors Suitable for Elaboration into a Functionalized Phenalene-type Tricyclic Skeleton.

The earlier results with the phenalenium cation[49,51] and the phenalenyl anion[47,49] make it clear that any synthetic strategy for preparing 13-methylphenalene XXIII must incorporate the central methyl group early in the synthesis. Figure 9 shows four possible compounds which are felt would make suitable precursors for an entry to the 13-methylphenalene nucleus.

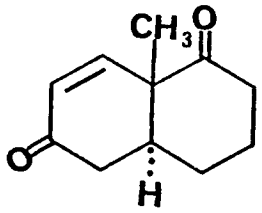
These precursors are all seen to possess the central angular methyl group, and suitable functionalization to allow relatively simple annelation of the third ring necessary for the formation of the phenalene nucleus. In diene ester XXXIV a long range plan for forming the tricyclic skeleton would involve protection of the ketone as the ethylene ketal, reduction of the ester to the primary alcohol, preparation of the chloride or bromide, and then two carbon extension with reagents like acetaldehyde cyclohexylimine[55] or cis-2-ethoxyvinyllithium.[56] After removal of the ketal an aldol cyclization would produce a useful tricyclic intermediate. This general plan is illustrated in Scheme I.



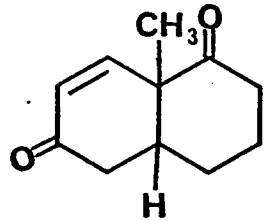
XXXIV



XXXV

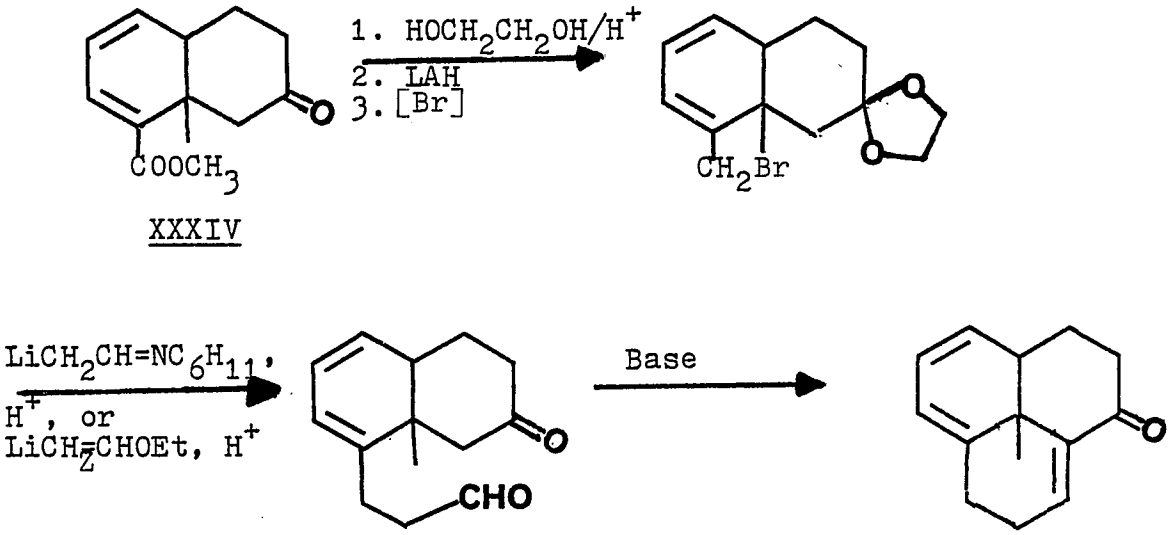


XXXVI



XXXVII

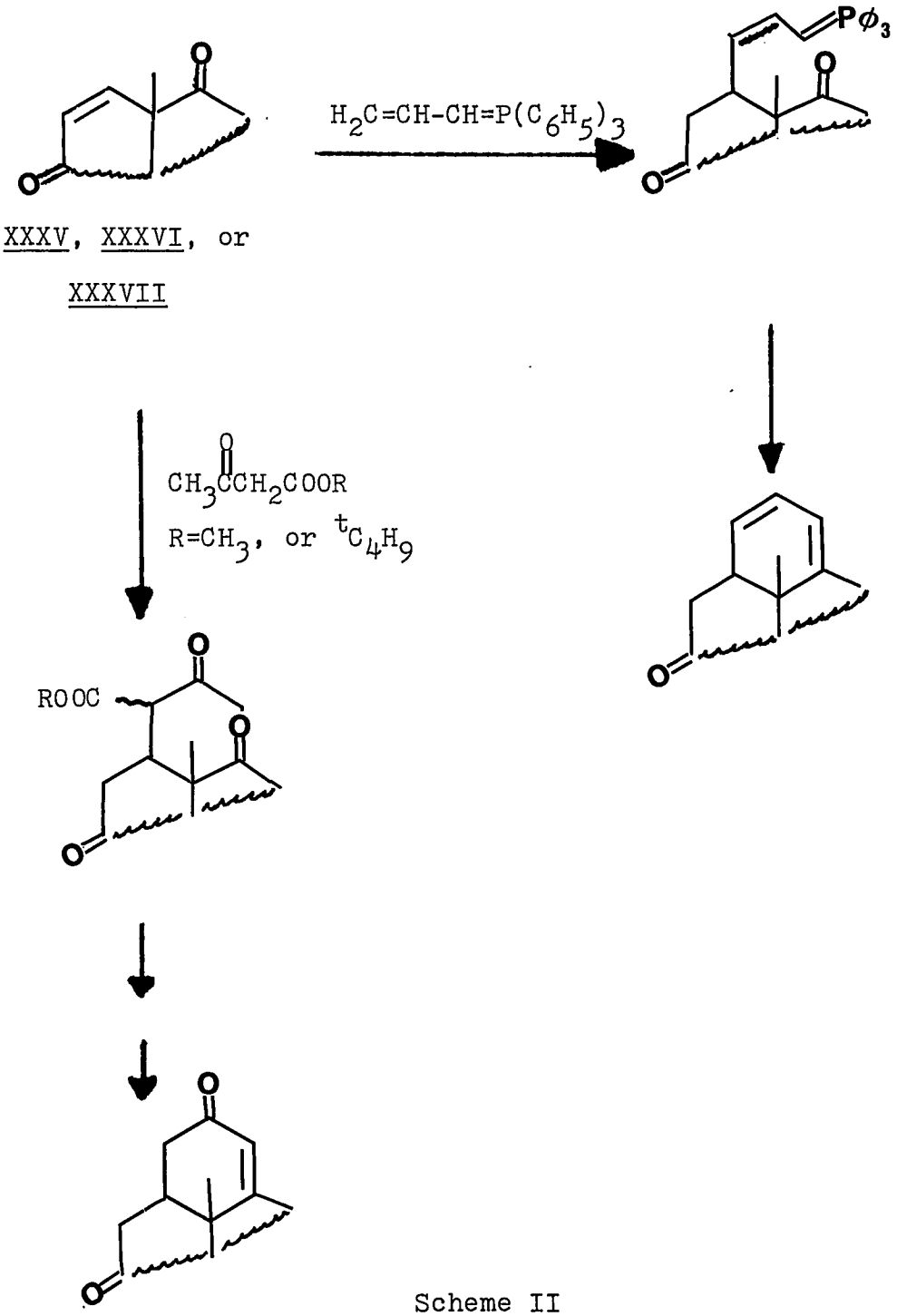
Figure 9. Four Potential Precursors Suitable For Elaboration Into a Phenalene Nucleus.



XXXIV

Scheme I

For compounds XXXV, XXXVI, and XXXVII the strategy would be similar for annelation of the third ring. This would involve a Michael reaction with a three carbon synthon such as allylidenetriphenylphosphorane, methyl acetoacetate, or t-butyl acetoacetate, at the less hindered double bond in XXXV and at the Δ^1-double bond in XXXVI and XXXVII. For the ester synthons the ring closure would be effected after ester hydrolysis and decarboxylation. The phosphorane annelation would involve addition of the phosphorane from the γ position to the α,β-unsaturated ketone and then an intramolecular Wittig reaction. These approaches are illustrated in Scheme II.


H2C=CH-CH=P(C6H5)3
Pφ3
XXXV, XXXVI, or
XXXVII
CH3CCH2COOR
R=CH3, or tC4H9
ROOC

Scheme II

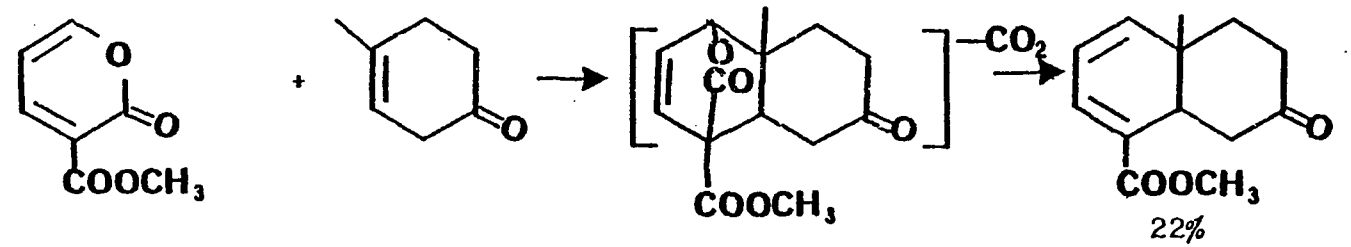
1. Attempted Synthesis of Keto Ester XXXIV.

Corey and Watt have reported the successful Diels-Alder reaction between 4-methyl-3-cyclohexenone and 3-carbomethoxy-2-pyrone XXXVIII to yield a highly functionalized keto ester in 22% yield, (eq 8).[57] The Diels-Alder reaction between pyrone XXXVIII and 3-methyl-3-cyclohexenone XXXIX should produce keto ester XXXIV, (eq 9).

3-Methyl-3-cyclohexenone XXXIX was synthesized by modifications of the Birch procedure.[58] Standard Birch reduction of m-methylanisole XL with sodium in liquid ammonia afforded an 83.4% yield of 1-methoxy-5-methyl-1,4-cyclohexadiene XLI, (eq 10).[58] Careful ketalization of the enol ether XLI with p-toluenesulfonic acid in methanol afforded a 75.4% yield of ketal XLII. Ketal XLII was carefully hydrolyzed with 1% hydrochloric acid for 0.5 h to yield the desired enone XXXIX. Isomerization of the γ,δ-enone to the α,β-enone occurs upon exposure to stronger acids for longer times.[59] This method produced the enone XXXIX in a pure state by GC analysis.

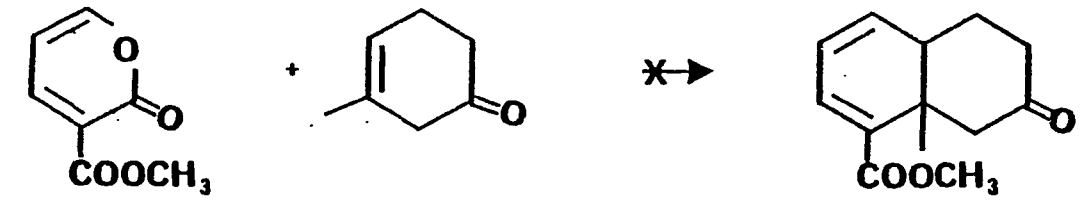
Pyrone XXXVIII was synthesized by standard techniques.[57,60] Acid catalyzed Knoevenagel condensation of tetramethoxypropane XLIII with dimethylmalonate XLIV yielded the allylidenemalonate XLV in 72.8% yield, (eq 11). Malonate XLV was cyclized with 90% formic acid to the desired 3-carbomethoxy-2-pyrone XXXVIII in 57.1% yield, (eq 11).

Unfortunately, XXXVIII and XXXIX could not be induced to



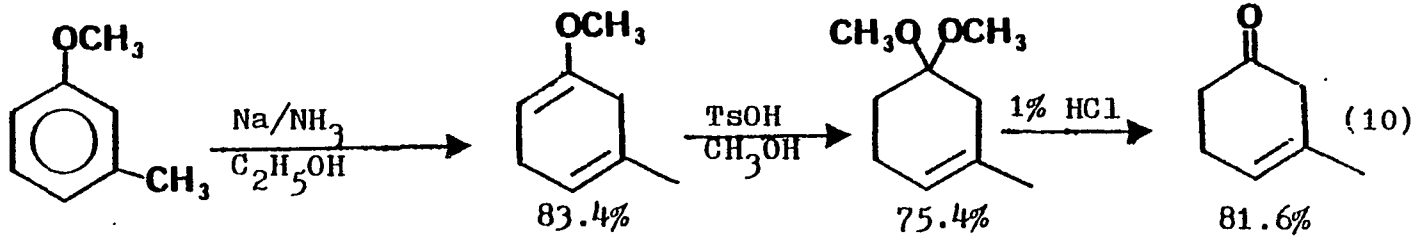
(8)

XXXVIII



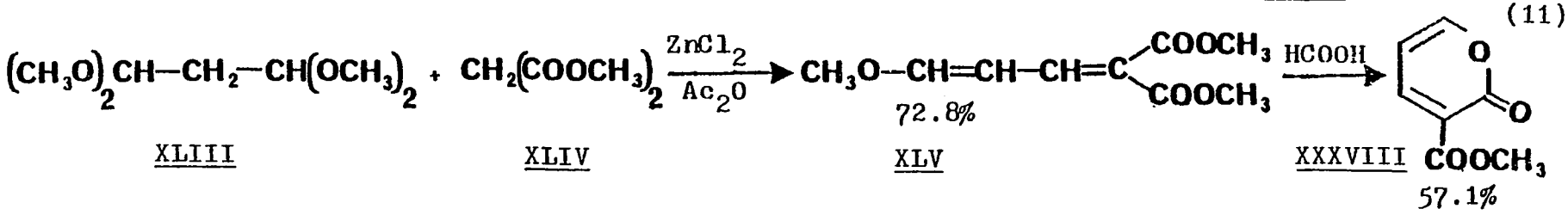
(9)

XXXVIII XXXIX XXXIV



(10)

XL XLI XLII XXXIX



(11)

XLIII XLIV XLV XXXVIII

undergo the Diels-Alder reaction under variety of conditions, (Table 1).

Table 1

Attempted Diels-Alder Reaction between XXXVIII and XXXIX.

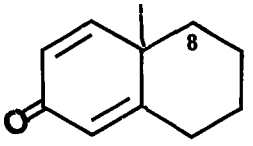
Run	Conditions	Solvent	Catalyst
1	Sublimed XXXVIII 140-150°C, 24 h	none	none
2	Unsublimed XXXVIII 140-150°C, 24 h	none	none
3	Unsublimed XXXVIII 130-140°C, 48 h	Chlorobenzene	none
4	Unsublimed XXXVIII 110°C, 24 h	Chlorobenzene	$AlCl_3$
5	Unsublimed XXXVIII 95°C, 24 h	Chlorobenzene	$SnCl_4$
6	Unsublimed XXXVIII 90-120°C, 24 h	none	$SnCl_4$

The reason for the failure of this reaction may be due to a severe steric interaction in the transition state between the carbomethoxy group in XXXVIII and the methyl group in XXXIX. This line of research was then abandoned.

2. Attempted Synthesis of Cross-Conjugated Dienedione XXXV.

Cross-conjugated cyclohexadienedione XXXV seemed to offer good possibility as a precursor for a tricyclic intermediate

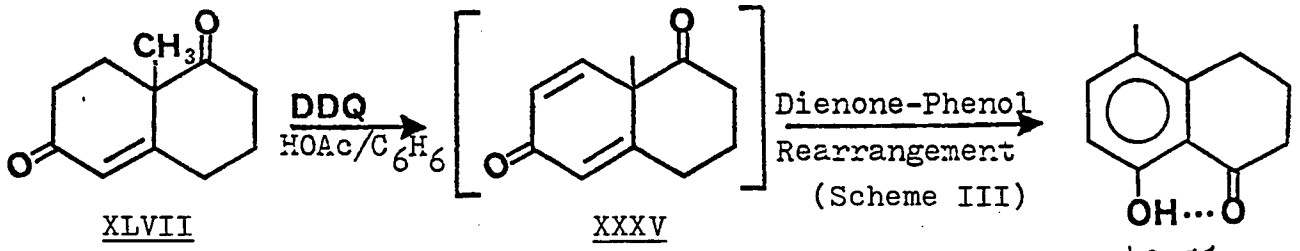
because of its varied and well placed functionality. There are no known systems like XXXV with a C_8-keto group. Woodward and Singh have synthesized cross-conjugated cyclohexadienone XLVI, a closely related system.[61]



XLVI

The most direct approach to XXXV appeared to be the 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)[62] mediated oxidation of the Wieland-Miescher ketone XLVII,[63] (eq 12). Using the general procedure of Kropp, XLVII was treated with excess DDQ and a catalytic amount of glacial acetic acid in dry benzene.[64] The only product observed from this reaction was the known 5-methyl-8-hydroxy-1-tetralone XLVIII[65] in 40-45% yield in small scale experiments. When the experiment was repeated without the acid catalyst, the identical result was observed, but the yield was only 20%. The presumed dienone-phenol rearrangement[66] could not be prevented. The mechanism for this rearrangement on the intermediate XXXV is shown in Scheme III.

The spectral data for XLVIII was in excellent agreement with published spectra.[65] The isomeric and known 8-methyl-5-

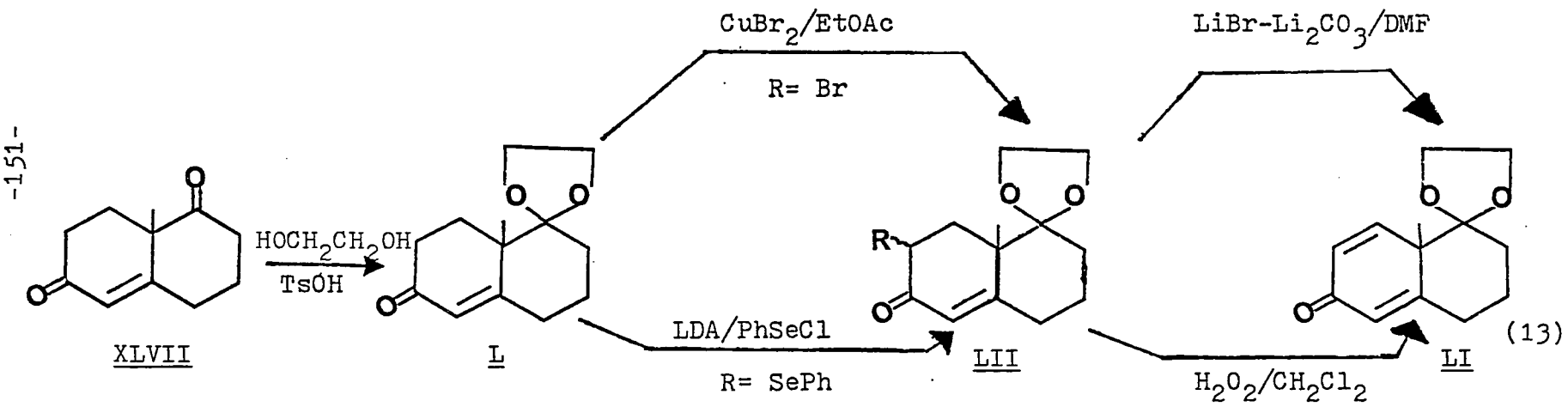


XLVII XXXV

40-5%
mp 48-50°

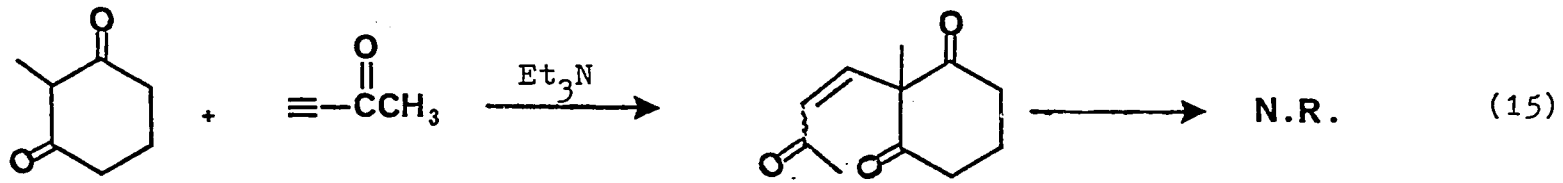
XLVIII

(12)

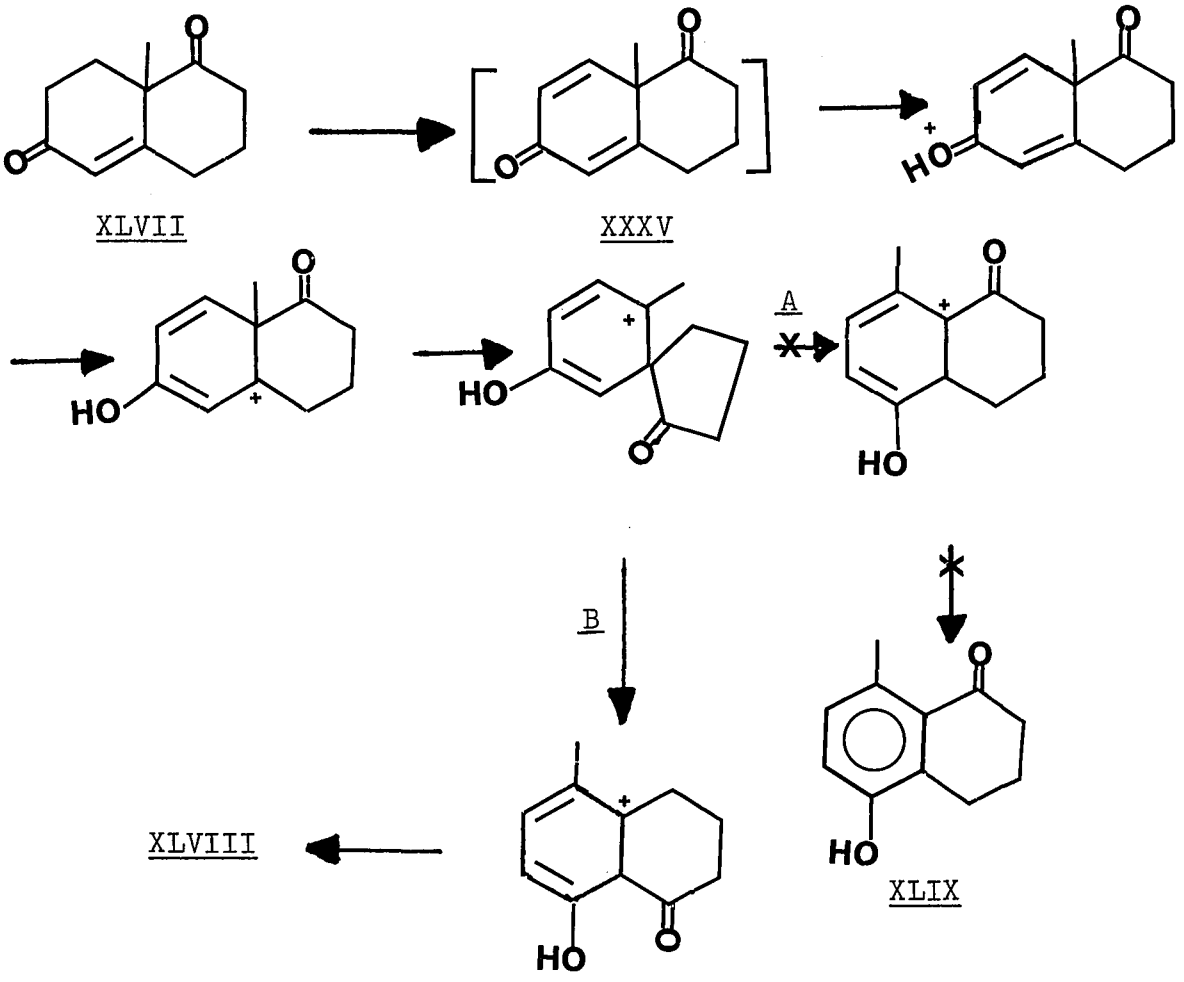


XLVII L LII LI

(13)



(15)



Scheme III

hydroxy-1-tetralone XLIX[67] was not detected. This is apparent from unfavorable pathway A where a carbonium ion is α to a carbonyl group.

Selenium dioxide oxidation of XLVII failed to give any product that could be characterized as XXXV.[68]

The saturated carbonyl in XLVII was protected as the ethylene ketal L, (eq 13), using standard techniques,[63b,69] but this

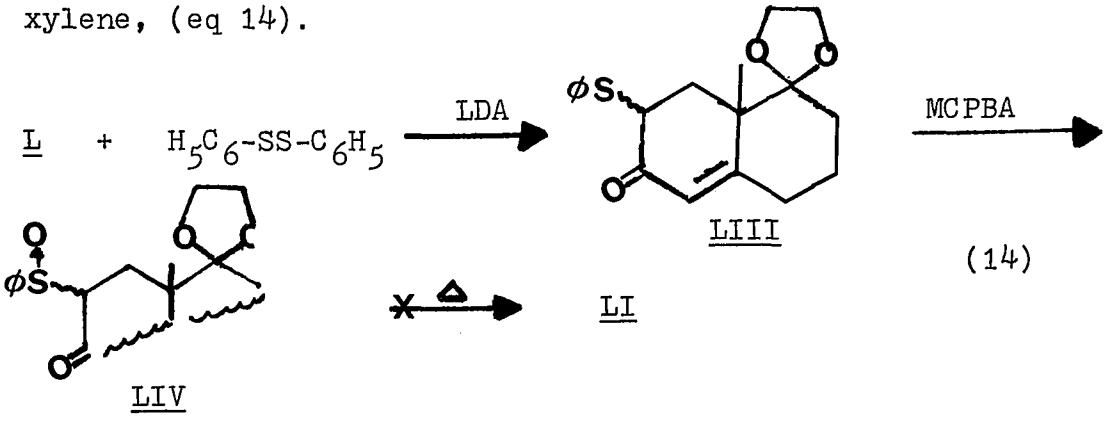
compound failed to react with DDQ.

3. Attempted Synthesis of XXXV Through Keto-Ketal LI.

Two methods were used to introduce the Δ^1 double bond in L. The first of these involved bromination of L with cupric bromide in chloroform-ethyl acetate,[70] (eq 13). The crude bromide LII (R=Br) was allowed to react with lithium bromide and lithium carbonate in dry DMF at approximately 130°C.[71] The cross conjugated keto-ketal LI obtained in this way could be distilled, albeit in modest yield, (eq 13). Attempts at hydrolyzing the ketal group in LI to get XXXV failed. As the hydrolysis proceeded, there was a gradual loss of the ^{1}H-NMR signals from the vinylic protons.

The second method of preparation of LI involved formation of the homoannular dienolate anion [72] of L with lithium diisopropylamide (LDA) and trapping of this enolate with phenylselenenyl chloride according to the general procedure of Reich et al.[73], forming the α-phenylseleno ketone LII (R=SePh), (eq 13). Crude selenide LII (R=SePh) was allowed to react with hydrogen peroxide in dichloromethane or ethyl acetate, affording the desired cross-conjugated ketal LI along with unchanged L, (eq 13).[73] Although LI was stable it resisted all forms of purification when prepared by the Reich procedure.[73, 74] Again attempted hydrolysis of the mixture of L and LI resulted in the decomposition of LI.

In addition L was sulfenylated with phenyl disulfide according to the Trost procedure.[75] The α-phenylthio ketone LIII was oxidized with m-chloroperbenzoic acid (MCPBA) or sodium metaperiodate to the sulfoxide LIV. This sulfoxide could not be dehydrosulfenylated by heating in toluene or xylene, (eq 14).



(14)

4. Attempted Preparation of XXXV Through a Robinson Annelation.

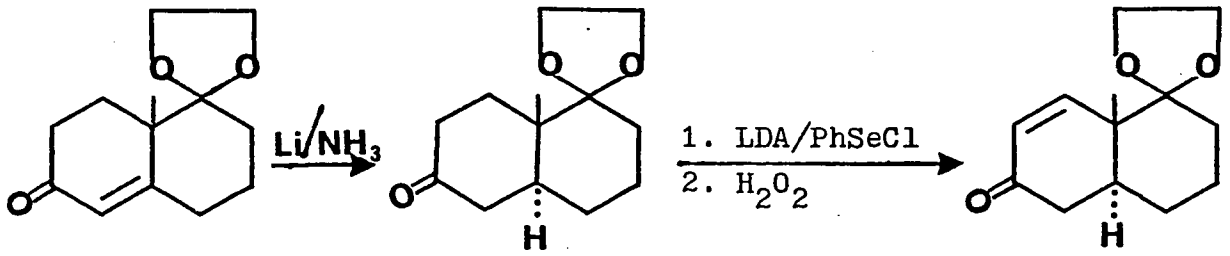
Because of Woodward's success in preparing XLVI by a Robinson annelation[61] of 2-methylcyclohexanone and 3-butyne-2-one, the analogous reaction of 2-methyl-1,3-cyclohexanedione seemed appropriate.[76] From an analysis of the ^{1}H-NMR spectrum, the initial Michael reaction appeared to occur in moderate yield, (eq 15). Unfortunately, the crude Michael adduct could not be cyclized under a variety of basic conditions (KOH, triethylamine). If the Michael adduct in eq 15 has a trans cofiguration about the double bond, than an aldol condensation would be geometrically impossible.

5. Preparation of Crude trans-ketal LV.

A transposition of the double bond in L was accomplished by lithium/ammonia reduction of L to trans-ketal LVI.[69b] This compound was selenenyated and dehydroselenenyated using the procedure of Reich and co-workers.[73] TLC indicated the formation of LV, (eq 16), along with starting material (L). The formation of L from LVI indicates that the enolate generated from LVI was not generated regiospecifically. ^{1}H-NMR indicated the formation of the new enone system in LV along with starting L, (eq 16). This method did not appear practicable for large scale synthesis, so it also was abandoned.

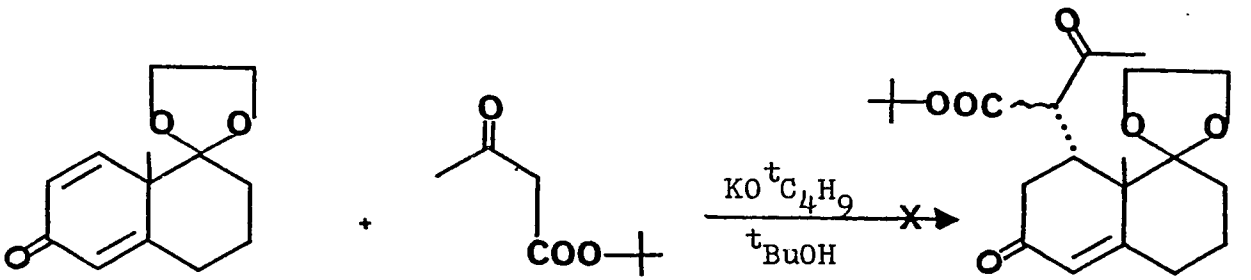
6. Attempted Preparation of Michael Adduct LVII.

Crude dienone ketal LI and tert-butyl acetoacetate LVIII, (eq 17) were treated with a catalytic amount of potassium tert-butoxide in t-butyl alcohol in order to effect a Michael reaction at the Δ^1 double bond. After 72 h at 80°C no reaction was observed. ^{1}H-NMR showed only the presence of starting material. Ketal LI probably suffers severe steric crowding between the ketal group and the tert-butyl side chain in LVIII which prevents the formation of LVII, (eq 17).



(16)

L LVI LV + L

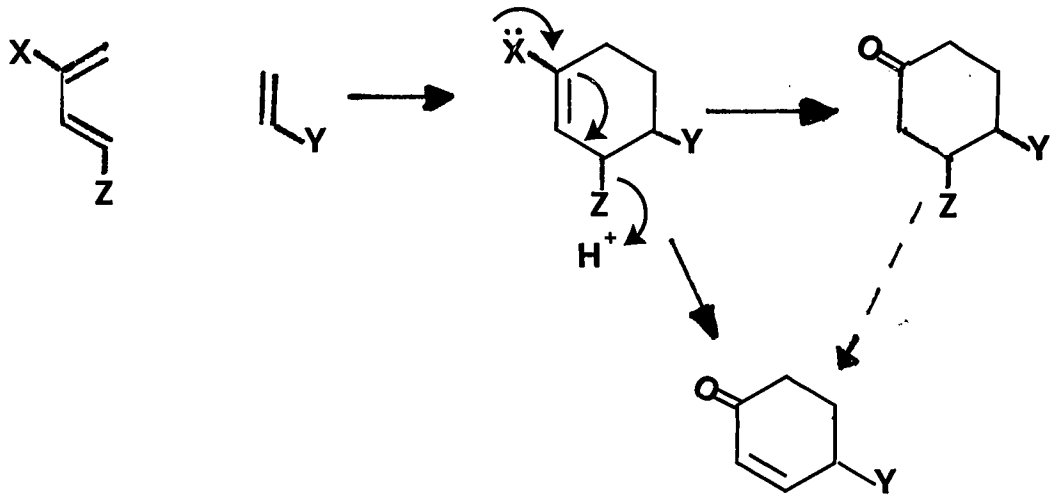


(17)

LI LVIII LVII

7. Synthesis of cis-Δ^1-3-octalone XXXVII.

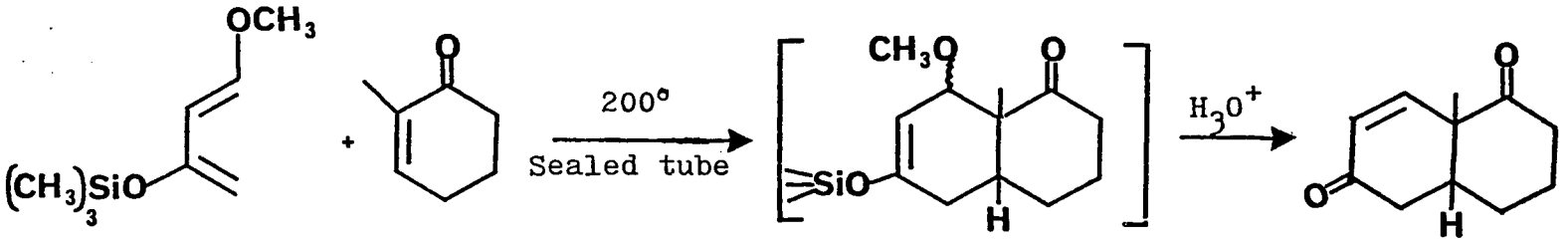
Danishefsky and Kitahara have recently introduced a Diels-Alder diene which permits the synthesis of XXXVII,[77] the final synthon that was expected to make a suitable intermediate to build a tricyclic structure. The principles that Danishefsky uses are outlined in Scheme IV.[77]



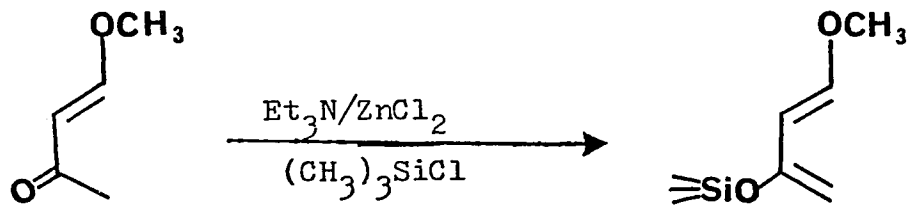
Scheme IV[77]

X and Y in the diene component should allow for high reactivity and high orientational specificity with unsymmetrical and unactivated dienophiles. To accomplish this Y should be an electron withdrawing group, X should be suitable for conversion from an enol ether to a carbonyl, and Z should be capable of entering into a β-elimination. Thus after hydrolysis of the initial Diels-Alder product with acid it should be possible to produce an enone system as in Scheme IV.

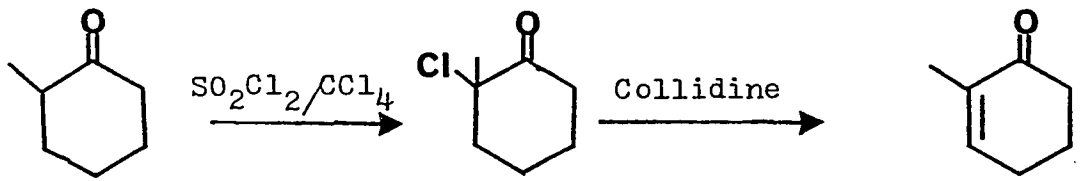
In the event Danishefsky and Kitahara[78] were indeed able to synthesize cis-Δ^1-3-octalone XXXVII as illustrated in eq 18. The diene component, trans-1-methoxy-3-trimethylsilyloxy-1,3-butadiene LIX was synthesized by vinylogous silylation of the commercially available trans-4-methoxy-3-buten-2-one LX using zinc chloride and triethylamine, (eq 19).[77] 2-Methyl-2-cyclohexenone LXI was synthesized by chlorination of LXII with sulfuryl chloride and then dehydrochlorination with collidine at 150°C, (eq 20).[79] In small scale experiments the yield of the octalone XXXVII was 45-50%, but in large scale experiments the yield was only 20-38%. The large scale reactions were run for 48 h rather than the reported 24 h.[78] Using a solvent such as p-xylene did not improve the yield. A catalytic amount of hydroquinone was used to stabilize the diene component. Using this method relatively large amounts (10-20 g) of the octalone XXXVII could be synthesized. With a suitable precursor now in hand, the synthesis turned to the task of annelating the third ring onto octalone XXXVII.



LIX LXI XXXVII (18)



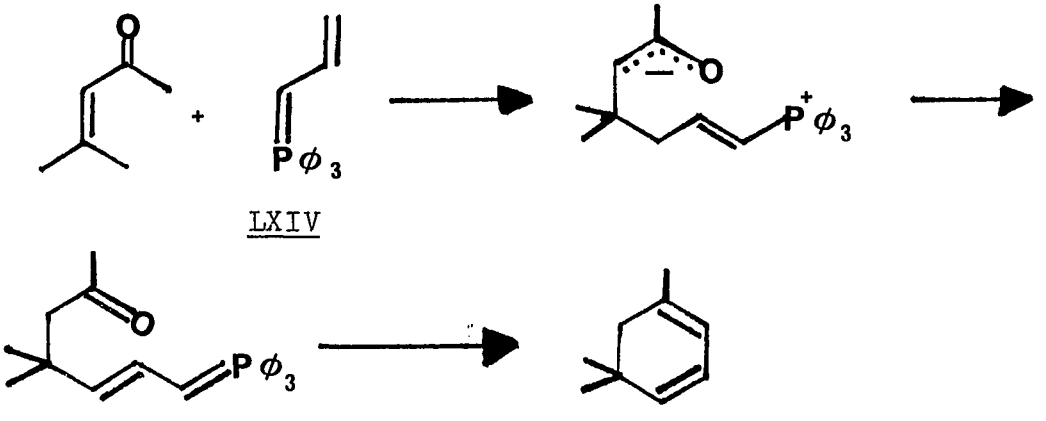
LX LIX (19)



LXII LXI (20)

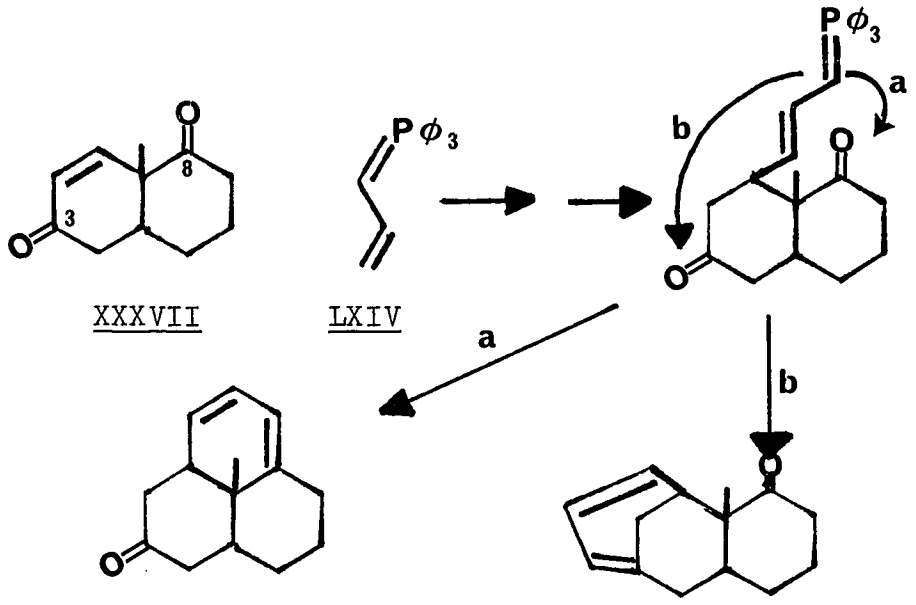
B. Synthesis of the Key Tricyclic Intermediate 13-Methyl-3,4,5,6,7,8,9,10,11,12,13-undecahydro-3,7-phenalenedione LXIII,[80] a Functionalized 13-Methylphenalene Intermediate.

A logical approach to dione LXIII, (eq 21), would involve a Michael reaction at the β position of the enone system in octalone XXXVII followed by an intramolecular condensation at C_8. What was needed was a three carbon synthon that could add under basic conditions to the enone system. Allylidenetriphenylphosphoranes are known to add from the the γ position of the ylid to the β carbon atom in enone systems and then suffer an intramolecular Wittig condensation with the now saturated ketone.[81] The principle is illustrated in Scheme V where allylidenetriphenylphosphorane LXIV adds in a conjugate fashion and from the γ position of the ylid to mesityl oxide.[81b]



Scheme V

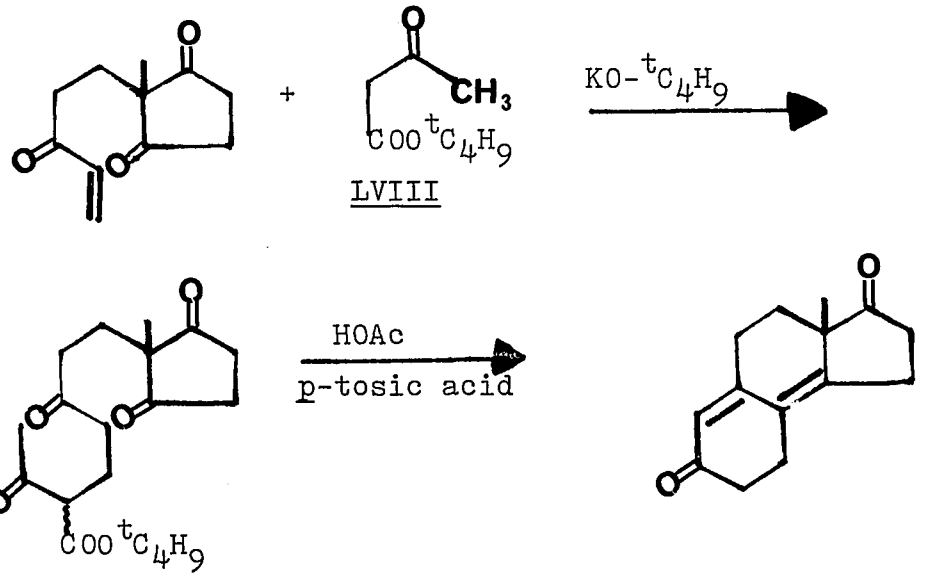
This approach allows formation of cyclohexadienes in moderate yields. Extrapolating this method to octalone XXXVII, allylidenetriphenylphosphorane LXIV would be expected to add in an analogous manner to octalone XXXVII and then cyclize by Wittig condensation at C_8. The Wittig reaction was not expected to occur at C_3 (Scheme VI, path b) because this would result in the formation of a bridgehead double bond and a very strained cyclohexadiene, whereas reaction at C_8 (Scheme VI, path a) would be expected to produce a less strained system. In the event that no choice is possible in the intramolecular Wittig condensation, formation of bridgehead olefins has been noted by Dauben.[81c] The approach utilizing octalone XXXVII is illustrated in Scheme VI.



Scheme VI

In the event the octalone XXXVII was totally unreactive with the ylid LXIV. Therefore, a different three carbon synthon would have to be used.

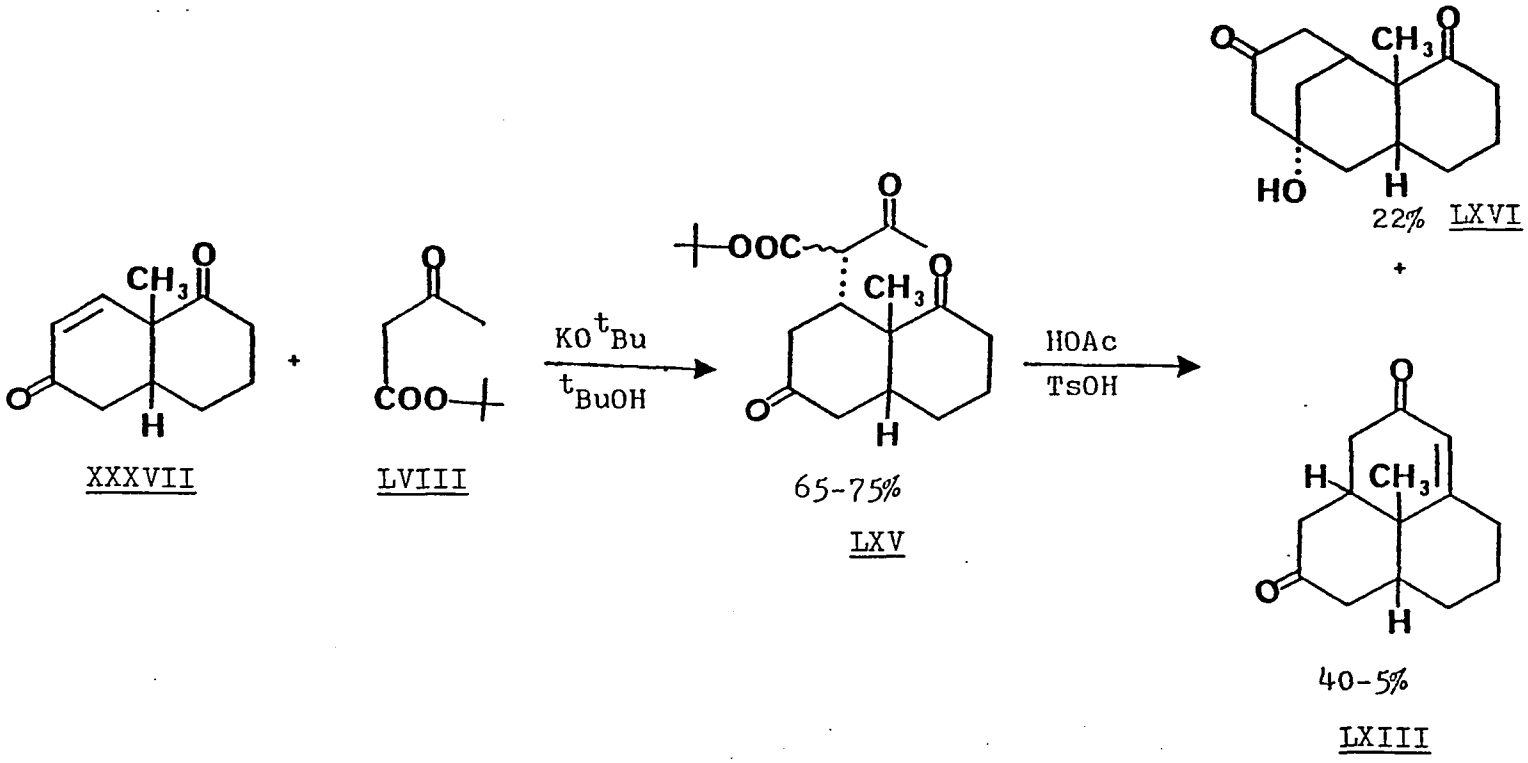
Danishefsky and Migdalof reported an interesting cyclization reaction using tert-butyl acetoacetate LVIII and an enone system.[82] The condensation and cyclization are shown in Scheme VII.



Scheme VII

This reaction can be seen as a Michael reaction of the ester on the enone system, and then subsequent cyclization. This strategy can be applied to octalone XXXVII to obtain a functionalized tricyclic intermediate.

Treatment of octalone XXXVII with tert-butyl acetoacetate LVIII and a catalytic amount of potassium tert-butoxide in t-butyl alcohol, (eq 21), cleanly produced the ester LXV in


CH3
O
H
XXXVII
+
COO
LVIII
KO tBu
tBuOH
OOC
65-75%
LXV
HOAc
TsOH
HO
22% LXVI
+
H
40-5%
LXIII

(21)

65-75% yield as a crystalline solid after work up. The key tricyclic compound LXIII was then obtained by treatment of ester LXV with a catalytic amount of p-toluenesulfonic acid in glacial acetic acid at 80°C for 2.5-3.5 h, essentially according to the procedure of Danishefsky and Migdalof.[82]

Tricycle LXIII was obtained consistently in 40-45% yield after purification by silica gel chromatography. This crystalline compound gave an elemental analysis and spectroscopic data consistent with the proposed structure. Formally the reactions that occurred were an aldol condensation with loss of water, an ester hydrolysis, and a decarboxylation.

Further elution of the silica gel column afforded the tricyclic alcohol LXVI in 20-22% yield, which was formed by an aldol condensation at the "wrong" carbonyl group. The elemental analysis and spectral data were in complete agreement with the assigned structure. The stereochemistry of the bridgehead alcohol was not determined.

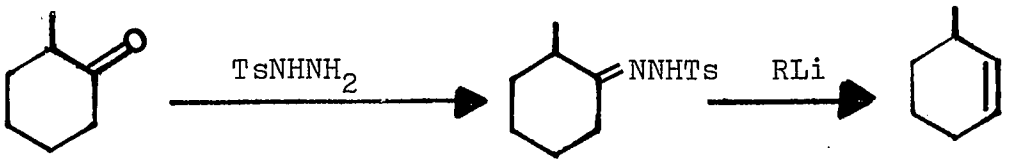
C. Synthesis of 13-Methyl-5,8,9,10,11,12,13-heptahydrophenalene LXVII.[83]

With useful quantities of the tricyclic enedione LXIII now in hand, the next phase in the synthesis involved the conversion of the saturated ketone and the α,β-unsaturated ketone into olefin groups. There are a number of methods available to the synthetic organic chemist to bring about this transformation. These methods include: 1. Formation of the tosylhydrazone and then treatment with an alkyllithium to form the olefin. 2. Formation of the tosylhydrazone and then treatment with lithium hydride to form the olefin. 3. Formation of an enol phosphate and then reductive cleavage with lithium in an organic amine. 4. Reduction of the carbonyl group(s) with sodium borohydride or other hydride reagent, and conversion of the alcohol to the olefin by dehydration, or conversion to the mesylate, tosylate, or halogen compound and treatment with base. Each of these methods has been investigated with tricycle LXIII and is discussed in the following sections.

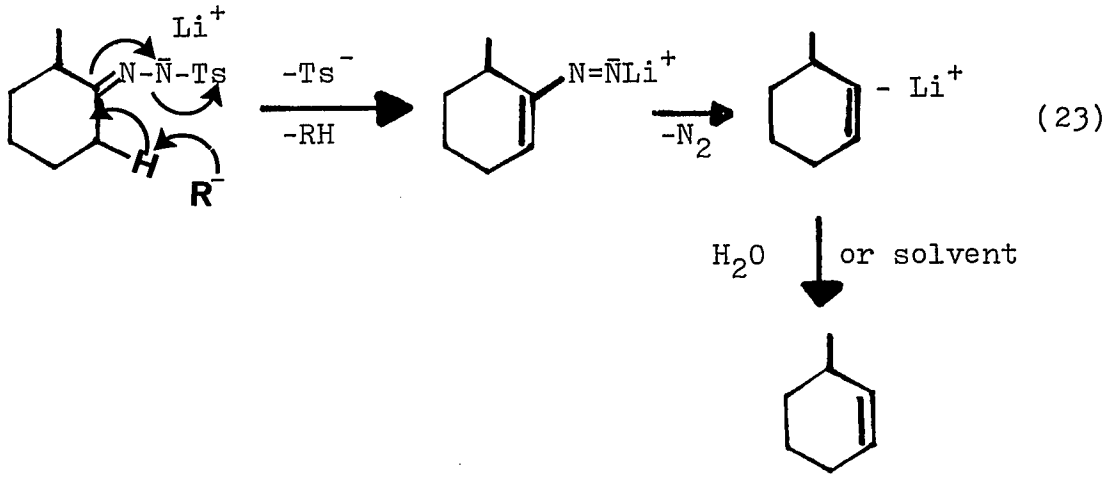
1. Attempted Synthesis of Triene LXVII Through Bis-tosylhydrazone LXVIII.

Shapiro and Heath reported the synthesis of olefins from saturated cycloalkanones by treatment of the tosylhydrazone

with an alkyllithium reagent.[84b] This approach is illustrated in eq 22 and the proposed mechanism[84b] is illustrated in eq 23.

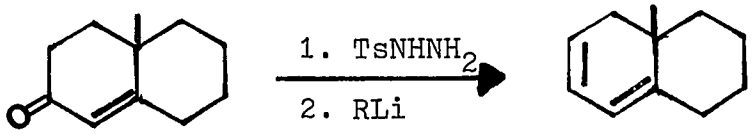


(22)



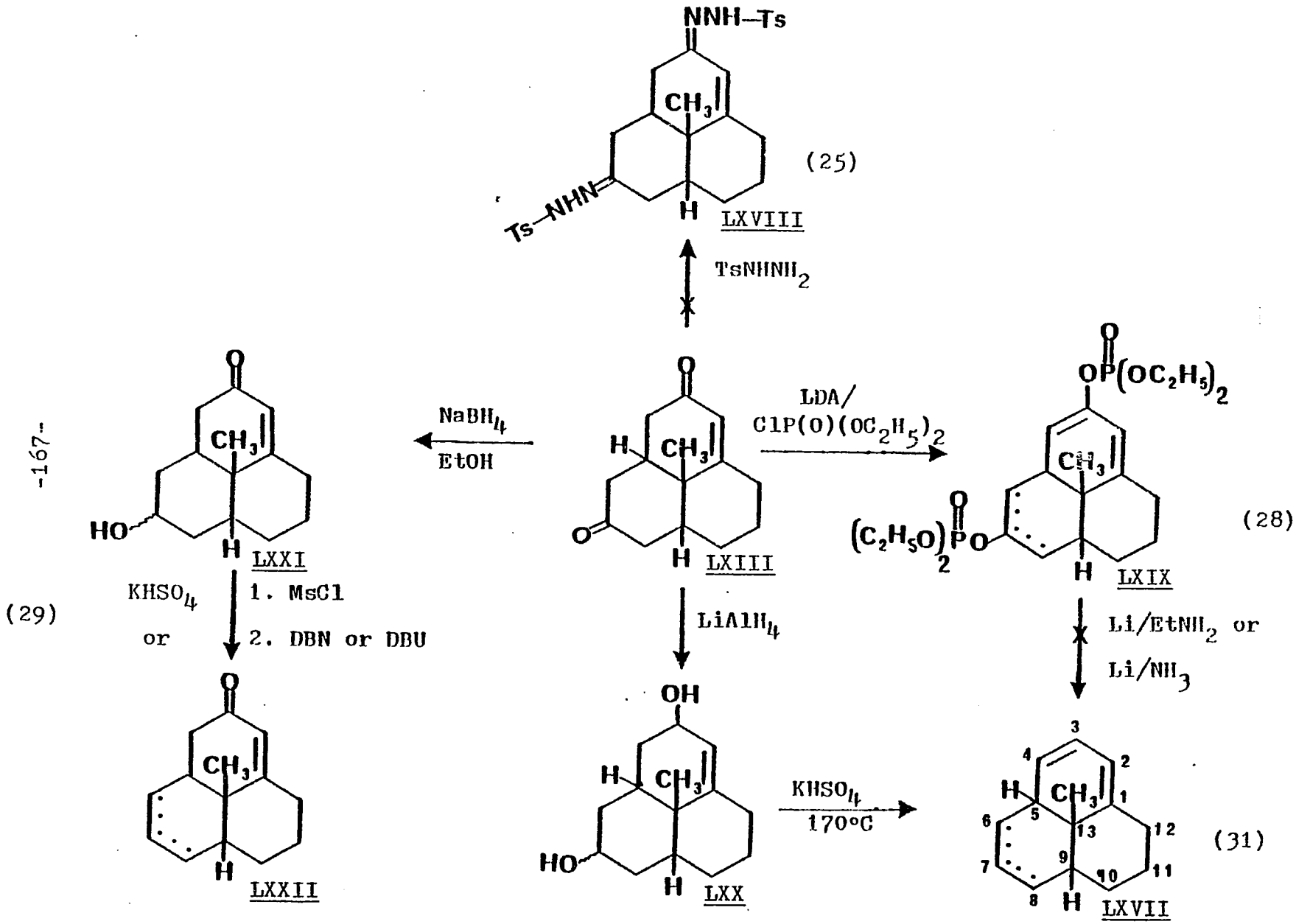
(23)

An extension of this method has been reported by Shapiro and co-workers.[84a] This involves formation of diene systems from α,β-unsaturated tosylhydrazones, (eq 24).



(24)

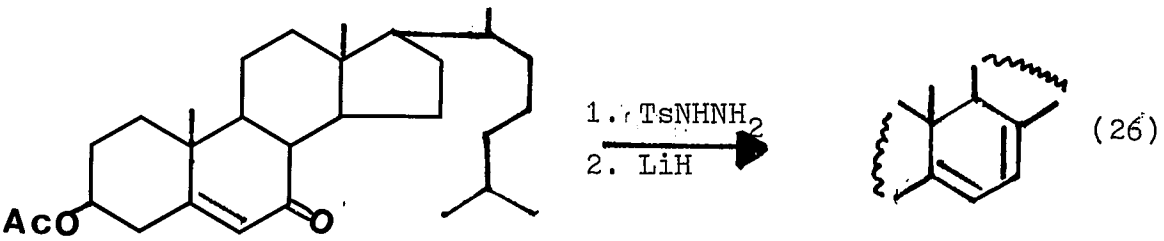
Since this method works with saturated as well as unsaturated ketones it seemed a good approach to try with enedione LXIII, which contains a saturated as well as unsaturated ketone.


NNH—Ts
CH3
Ts—NHN
H
LXVIII
(25)
TsNHNH2
NaBH4
EtOH
LDA/
ClP(O)(OC2H5)2
O
H
CH3
HO
LXXI
LXIII
OP(OC2H5)2
(C2H5O)2P
LXIX
(28)
KHSO4
or
1. MsCl
2. DBN or DBU
(29)
LiAlH4
Li/EtNH2 or
Li/NH3
OH
LXXII
LXX
KHSO4
170°C
LXVII
(31)

The preparation of bis-tosylhydrazone LXVIII was attempted using standard procedures.[84] Under a variety of conditions no isolated LXVIII could be obtained. TLC examination of the reaction mixture indicated a number of compounds, in addition to starting material. In fact the reaction mixture seemed sensitive to acid. When a catalytic amount of acid (one drop of concentrated hydrochloric acid) was introduced to the mixture of LXIII and recrystallized p-toluenesulfonylhydrazide in ethanol or methanol, the reaction mixture slowly darkened upon standing at ambient temperature for a few hours, and darkened rapidly when the mixture was refluxed. No reaction occurred when acid was not added. In any case the crude products when treated with excess methyllithium in ether failed to produce any characterizable products,[84] (eq 25).

2. Attempted Formation of Triene LXVII through Bis-tosylhydrazone LXVIII and Treatment with Lithium Hydride.

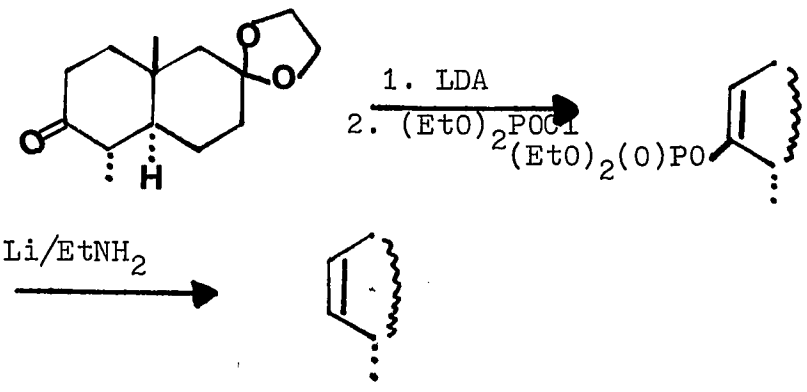
Caglioti and co-workers have reported the synthesis of 1,3-dienes by treatment of tosylhydrazones of α,β-unsaturated ketones with lithium hydride in toluene, (eq 25).[85] Using this approach on the crude (supposed) bis-tosylhydrazone LXVIII, no olefin could be detected in the reaction mixture. It appeared that no bis-tosylhydrazone was formed initially.



(26)

3. Attempted Formation of Triene LXVII Through Bis-enol phosphate LXIX.

Olefins have been prepared from ketones by forming the enolate anion with lithium diisopropylamide (LDA) and trapping the enolate with diethyl chlorophosphate. The enol phosphate is reductively cleaved with lithium in ammonia or ethylamine, (eq 27).[86,87] Unfortunately, there are no reports of this procedure being used on α,β-unsaturated ketones which would form a diene system. The tricyclic enedione LXIII was then subjected to this reaction sequence, (eq 28).



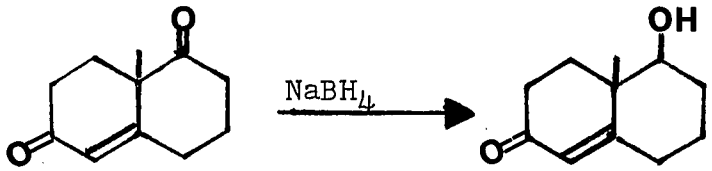
(27)[86b]

Tricyclic enedione LXIII was treated with lithium diisopropylamide in THF. The trienediolate dianion was then trapped with excess diethyl chlorophosphate. TLC, IR, and ^{1}H-NMR indicated the formation of the desired bis-enol phosphate LXIX along with unchanged starting material, (eq 28). The bis-enol phosphate LXIX was treated with lithium in ethylamine[86] or ammonia.[87] No products with the desired structure (LXVII) could be detected. ^{1}H-NMR revealed that over reduction had occurred because no vinylic signals could be detected. When the amount of lithium was reduced (from five equivalents per phosphate group to two equivalents per phosphate group) no reaction occurred. These results forced abandonment of this approach.

4. Formation of Triene LXVII through diol LXX.

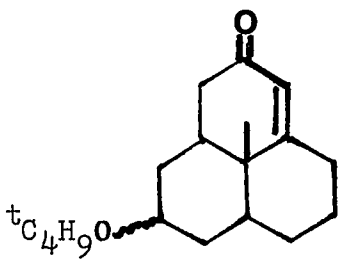
Tricyclic enedione LXIII was treated with excess sodium borohydride in 95% ethanol for 0.5 h at 0-5°C and for 0.5 h at ambient temperature. After hydrolysis of the borate ester with 10% acetic acid and extraction into ether, the hydroxy enone LXXI was isolated as a mixture of isomers in quantitative yield, (eq 29). The fact that the reduction had occurred only at the cyclohexanone carbonyl could be inferred from the strong IR absorption at 1670 cm^{-1} which indicated the presence of an α,β-unsaturated ketone. This result with sodium borohydride mimics that of Boyce and Whitehurst,[88] who obtained a similar

result in the reduction of the Wieland-Miescher ketone, (eq 30).



XLVII (30)

Hydroxy enone LXXI was mesylated with methanesulfonyl chloride in dry dimethoxyethane (DME) or THF with dry triethylamine.[89] The crude mesylate was treated with 1,5-diazabicyclo-(4.3.0)non-5-ene (DBN) or 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU) at ambient temperature, usually for a few hours.[90] This gave the dienone LXXII in moderate yield (ca.40% from LXXI), (eq 29). The ^{1}H-NMR spectrum revelaed the presence of three vinylic protons. The elimination reaction with potassium tert-butoxide in t-butyl alcohol proceeded much more slowly. The products from this reaction were the desired dienone LXXII and the tert-butoxy compound LXXIII. It is possible that a trans diaxial conformation is difficult to attain in LXXI and its mesylate; therefore, β-elimination would be difficult.

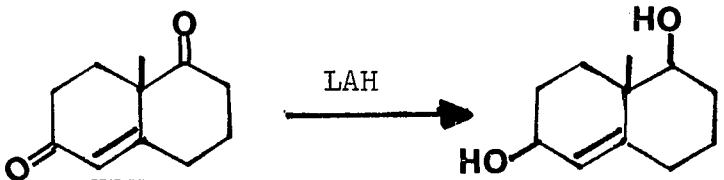


LXXIII

Further, the dienone LXXII could be obtained in better yield

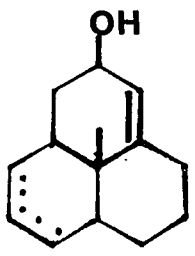
(ca. 80%) by treatment of hydroxy enone LXXI with potassium bisulfate[91] at 150°C (0.25 mm) in a typical E1 reaction,[92] (eq 29).

Tricyclic enedione LXIII was treated with lithium aluminum hydride (LAH) in dry ether to produce the tricyclic diol LXX. The yield was between 75-85%, after isolation by continuous extraction for at least 24 h, (eq 31). The formation of the diol LXX again parallels the results obtained by Boyce and Whitehurst[88] who obtained a diol of the Wieland-Miescher ketone by treatment with LAH, (eq 32).



XLVII (32)

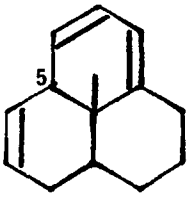
Tricyclic diol LXX was treated with potassium bisulfate[91] at 170°C (2.5 mm) which afforded 61.3% of a two component mixture after distillation. The mixture was separated by preparative TLC yielding 38.2% of the desired tricyclic triene LXVII and 10.2% of hydroxy diene LXXIV, (eq 31). Hydroxy diene LXXIV could be recycled to triene LXVII by treatment with potassium bisulfate.



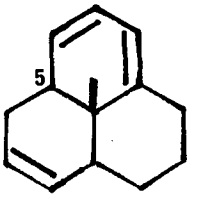
LXXIV

The ^{1}H-NMR spectrum (60 MHz) of tricyclic triene LXVII is shown in Figure 10. The spectrum is fully consistent with the assigned structure.

Since triene LXVII could dehydrate in a non-regiospecific manner to LXVIIa or LXVIIb, the ^{13}C-NMR spectrum of LXVII was determined in the expectation that it might provide information concerning the direction of elimination.



LXVIIa



LXVIIb

The proton decoupled ^{13}C-NMR spectrum of triene LXVII, (Figure 11), showed eight aliphatic carbons from δ 20.58-44.40 ppm (TMS internal standard). There were five olefinic carbons from δ 123.70 - 143.58 ppm. The olefinic carbon resonance at δ 124.14 ppm was approximately double the intensity of the other olefinic signals which may mean that there were two carbon signals at δ124.14 ppm. The spectrum was retaken in the gated decoupled mode with nuclear Overhauser effect, (Figure 12). When this was done the presence of two carbons could be inferred from the overlapping set of doublets (^{13}C-^{1}H coupling). Therefore, there are six olefinic carbons in agreement with the structure of LXVII.

The position of the double bond in LXVII is still in doubt.

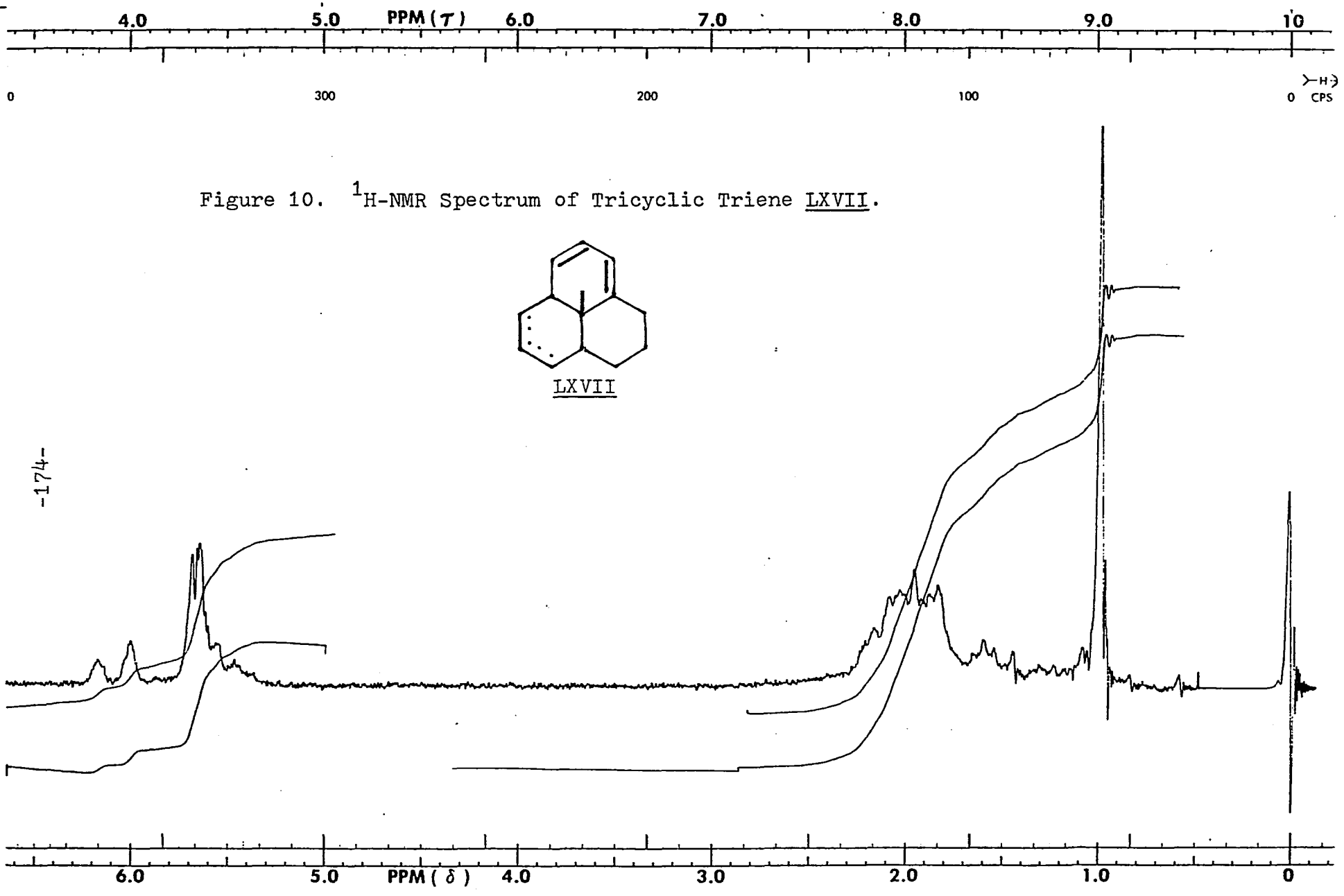


Figure 10. ^{1}H-NMR Spectrum of Tricyclic Triene LXVII.

LXVII

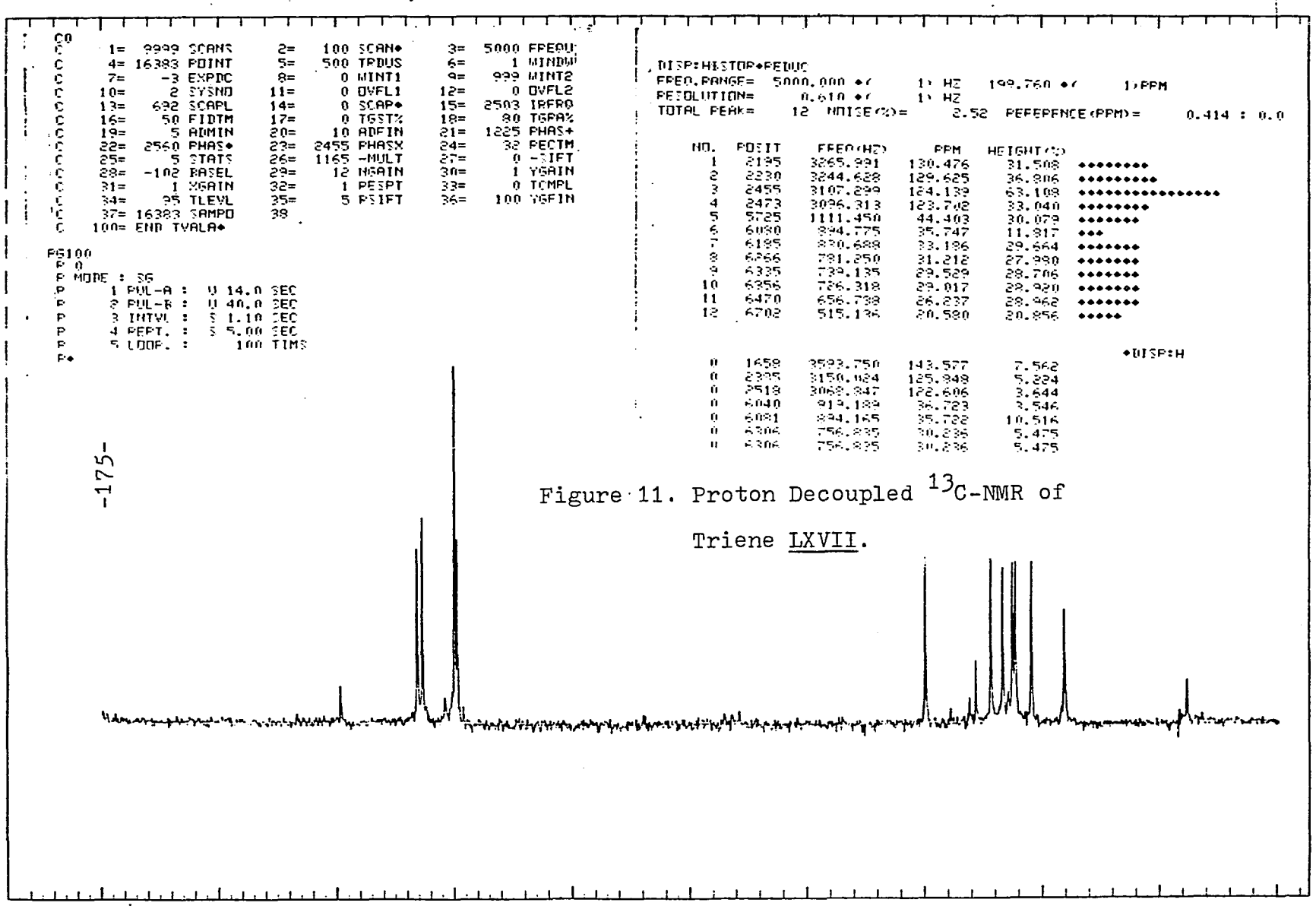


Figure 11. Proton Decoupled ^{13}C-NMR of Triene LXVII.

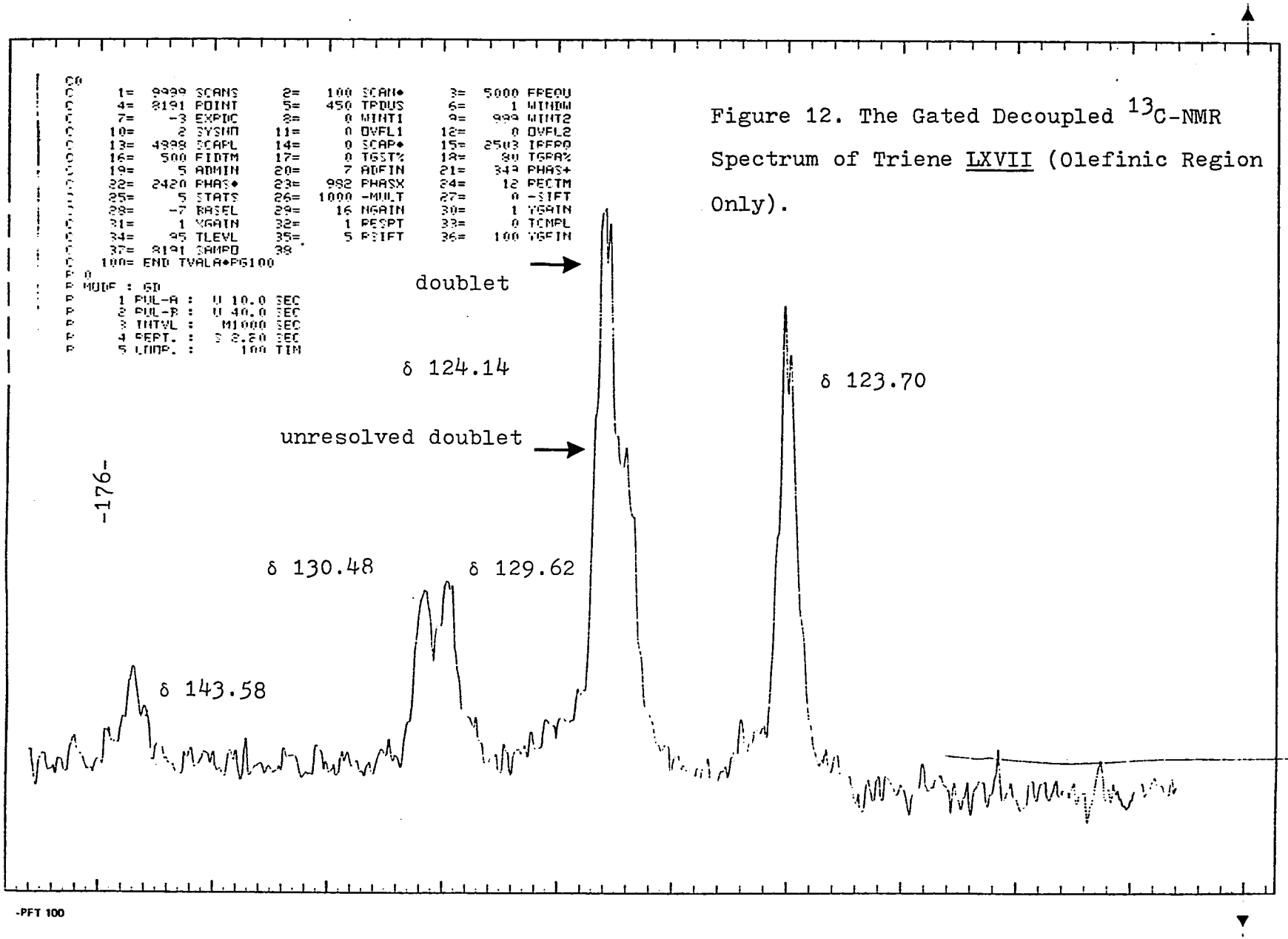
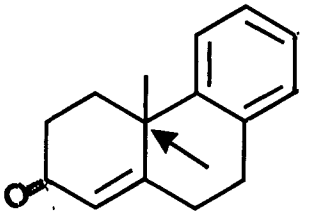


Figure 12. The Gated Decoupled ^{13}C-NMR Spectrum of Triene LXVII (Olefinic Region Only).

In LXVIIa C_5 is bis-allylic. The aliphatic carbon resonance in 1,4-cyclohexadiene appears at δ 26.0 ppm;[94] however the allylic-benzylic carbon in LXXV appears at δ 39.6 ppm.[95]



LXXV

Unfortunately no clear cut decision regarding the position of the double bond in LXVII can be made at this time.

Although the synthesis of 13-methylphenalene XXIII has not yet been achieved, the synthesis of tricyclic triene LXVII puts this goal well within reach.

Chapter Three

Experimental Section

1. Preparation of 1-Methoxy-5-methyl-1,4-cyclohexadiene XLI;[58]

A 2 L three necked round bottomed flask, fitted with an all glass mechanical stirrer, 250 mL dropping funnel, nitrogen inlet, and dry ice condenser, was charged with approximately 1 L of dry liquid ammonia. A solution of 20.50 g (0.168 mole) of m-methylanisole XL in 71.52 g (1.55 mole) of absolute ethanol was added over 0.5 h to the liquid ammonia maintained at -70°C. Sodium (23.69 g, 1.03 mole) was added to the rapidly stirred solution in small pieces. After the addition the mixture was refluxed for 1.5 h after which time the blue color disappeared. The ammonia was allowed to evaporate overnight. Ether (600 mL) and saturated sodium chloride (300 mL) were added. The layers were separated and the aqueous layer was extracted with a further 250 mL of ether. The combined ether extracts were washed with water, dried ($MgSO_4$), and concentrated *in vacuo*. Distillation of the residue afforded 17.3859 g (83.4%) of XLI. bp 55-56°C (13 mm), (lit.[58] bp 168-170°C (760 mm)); IR(neat); 3080, 3020, 2990, 1680, 1640, 1480, 1440, 1220, 1110, 1020 $cm.^{-1}$

NMR(CCl_4); δ 1.67 (s with fine splitting, 3H), 2.6 (m, 4H), 3.48 (s, 3H), 4.52 (m, 1H), 5.33 (m, 1H).

2. Preparation of 1,1-Dimethoxy-3-methyl-3-cyclohexene XLII:

A 500 mL round bottomed flask was charged with 14.74 g (0.11 mole) of 1-methoxy-5-methyl-1,4-cyclohexadiene XLI, 160 mL of absolute methanol, and 5.2 mg of p-toluenesulfonic acid. The solution was stirred overnight at ambient temperature. The solution was poured onto 200 mL of saturated sodium bicarbonate and extracted with ether (2x200 mL). The ether was dried ($MgSO_4$) and concentrated in vacuo. Distillation of the residue afforded the unknown ketal XLII, 13.06 g (75.4%). bp 63-66°C (12 mm): IR(neat): 3050, 3030, 2980, 2835, 1670, 1460, 1430, 1360, 1310, 1270, 1245, 1160, 1070, 850 $cm.^{-1}$ NMR(CCl_4); δ 1.5-2.2 (m, 9H), 3.12 (s, 6H), 5.3 (m, 1H).

3. Preparation of 3-Methyl-3-cyclohexenone XXXIX:[58]

A 1 L flask was charged with 22.67 g (0.145 mole) of 1,1-dimethoxy-3-methyl-3-cyclohexene XLII, 300 mL of THF, and 300 mL of 1% HCl. The mixture was stirred for 1 h at 0-5°C. The mixture was carefully poured onto cold saturated sodium bicarbonate (500 mL) and extracted with ether (300 mL). The ether was dried ($MgSO_4$) and concentrated in vacuo. Distillation of the residue afforded 13.02 g (81.6%) of XXXIX. bp 53-55°C (12 mm), (lit.[58] bp 70°C (18 mm)).
IR(CCl_4); 3040, 2970, 2930, 2850, 1710, 1650, 1440 $cm.^{-1}$
NMR(CCl_4); δ 1.72 (m, 3H), 2.32 (m, 4H), 2.67 (m, 2H), 5.6 (m, 1H).

4. Preparation of Dimethyl 3-Methoxyallylidenemalonate XLV:[57,60]

A 500 mL three necked round bottomed flask equipped with a magnetic stirrer, nitrogen inlet, condenser, and dropping funnel was charged with 0.3559 g of anhydrous zinc chloride, 115 mL of acetic anhydride, and 57.50 g (0.350 mole) of tetramethoxypropane XLIII. The mixture was brought to reflux, and 37.13 g (0.251 mole) of dimethyl malonate XLIV were added dropwise. The mixture was refluxed overnight. The reaction mixture was distilled at atmospheric pressure and then *in vacuo* to afford 36.57 g (72.8%) of XLV. bp 130-139°C (0.2 mm), (lit.[57] bp 130-139°C (0.65-0.75 mm)).
IR(neat); 3050, 3000, 1750, 1630, 1445, 1300, 1250, 1200, 1100, 1000 $cm.^{-1}$
NMR was not taken.

5. Preparation of 3-Carbomethoxy-2-pyrone XXXVIII:[57,60]

A 250 mL three necked round bottomed flask equipped with a nitrogen inlet, condenser, and dropping funnel was charged with 55 mL of 90% formic acid. Dimethyl 3-methoxyallylidenemalonate XLV (21.0 g, 0.105 mole) was added dropwise. The reaction mixture was refluxed for 1.25 h. Volatiles were removed *in vacuo* and the remaining residue was immediately distilled to afford 9.2385 g (57.1%) of XXXVIII. bp 130-140°C (2.5 mm),

(lit.[57] bp 140-148°C (0.75 mm)).

IR(neat); 1775, 1710, 1685, 1560, 1230, 1100 $cm.^{-1}$

NMR(CCl_4); δ 3.92 (s, 3H), 6.5 (dd, $1H_5$, $J_{4,5}$ = 5 Hz, $J_{5,6}$ = 7 Hz), 7.92 (dd, $1H_4$, $J_{4,5}$ = 5 Hz, $J_{4,6}$ = 2 Hz), 8.36 (dd, $1H_6$, $J_{5,6}$ = 7 Hz, $J_{4,6}$ = 2 Hz).

6. Attempted Preparation of Dienedione XXXV:

A 200 mL single necked round bottomed flask equipped with a magnetic stirring bar was charged with 1.8 g (0.01 mole) of octalindione XLVII[63] and 2.86 g (0.0126 mole) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. Glacial acetic acid (5 mL) and 70 mL of dry benzene were added. The reaction mixture was blanketed with nitrogen and refluxed for 41 h. TLC showed some starting material and a new compound. The flask was cooled and solids were removed by filtration. The benzene layer was washed with sodium bicarbonate (100 mL) and water. After drying ($MgSO_4$) and concentrating *in vacuo* the residue was chromatographed on alumina II and eluted with benzene and then ether. An homogeneous oil (TLC) was obtained, 0.8022 g (45.1%). The yellow oil was crystallized from petroleum ether/ether. Spectral data indicated the compound to be 5-methyl-8-hydroxy-1-tetralone XLVIII.[65] mp 47-50°C (lit.[65] 47-48.5°C); IR(CCl_4); 2955, 2880, 1710(shoulder), 1630, 1465, 1345, 1240, 1225 $cm.^{-1}$

NMR(CCl_4); δ 2.0 (m, 2H), 2.12 (s, 3H), 2.55 (m, 4H), 6.55

(d, 1H, J = 8 Hz), 7.09 (d, 1H, J = 8 Hz), 12.37 (s, 1H exchanges with D_2O).
MS(70 eV); 176 (M^+), 148, 120 (base), 91, 77.

7. Preparation of Monoketal L:

i. By the Corey Procedure:[63b]

A single necked 500 mL round bottomed flask was charged with 250 mL of benzene and 70.17 g (1.132 mole) of ethylene glycol. The solution was refluxed under a Dean-Stark trap until no more water was collected. Octalindione XLVII (20.12 g, 0.113 mole) and 0.2114 g of p-toluenesulfonic acid were added. The reaction mixture was refluxed under a Dean-Stark trap until approximately 2 mL of water were collected. After cooling the reaction mixture was washed sequentially with saturated sodium bicarbonate (200 mL), brine (200 mL), and water (200 mL). The benzene layer was dried ($MgSO_4$) and concentrated in vacuo. The remaining oil was chromatographed on alumina II and eluted with benzene and then benzene-ether (1:1). A middle fraction afforded 15.95 g (66.2%) of the monoketal L. mp(EtOAc) 66-67°C, (lit.[63b] mp 66-67°C).
IR(CCl_4); 3025(shoulder), 2960, 2880, 1680, 1660, 1610, 1460, 1440, 1420, 1270, 1240, 1150, 1050 $cm.^{-1}$
NMR(CCl_4); δ 1.3 (s, 3H), 1.7 (m, 4H), 2.25 (m, 6H), 3.88 (s, 4H), 5.62 (s, 1H).

ii. By Transketalization with 2-butanone ethylene ketal.[69b]

A flask was charged with 26.64 g (0.149 mole) of octalindione XLVII, 93.41 g (0.805 mole) of 2-butanone ethylene ketal,[69b] 1.93 g (0.031 mole) of ethylene glycol, and 0.5043 g of p-toluenesulfonic acid. The contents were stirred at ambient temperature for approximately 26 h, then treated with 2 mL of triethylamine and diluted with 200 mL of benzene. The benzene solution was washed with water and dried ($MgSO_4$). Volatiles were removed in vacuo and the residue was chromatographed on alumina II and eluted with 30% ether in petroleum ether. This afforded 19.6 g (61%) of the monoketal L identical with the material prepared in i.

8. Preparation of Bromo Ketal (R=Br) LII:

A 100 mL three necked round bottomed flask fitted with a condenser, nitrogen inlet reaching to the bottom of the flask, and a calcium chloride drying tube was charged with 1.1534 g (0.0052 mole) of monoketal L, 35 mL of dry chloroform and 35 mL of dry ethyl acetate. With nitrogen bubbled through the solution, the flask was heated to 75-80°C and 2.3644 g (0.01 mole) of cupric bromide was added portionwise over a 2 h period. After the addition the flask was heated for 2 h. The tan precipitate of cuprous bromide was removed by filtration and solvents were removed in vacuo. The residue was taken up in ether and washed with water, sodium bicarbonate, and brine. The ether solution was dried ($MgSO_4$) and concentrated in vacuo

to afford a quantitative yield of LII (R=Br). This material was not purified further. IR was not taken. NMR(CCl_4); δ 1.2 (m, 3H), 2.3 (m, 8H), 3.5 and 4.3 (two sets of t, 4H, J = 6 Hz), 3.95 (m, 1H), 5.75 (s, 1H).

9. Preparation of Cross-Conjugated Ketal LI From Bromo Ketal LII (R=Br):

The method of R. Jolly was followed with slight modifications.[93] A 100 mL three necked round bottomed flask equipped with a magnetic stirring bar, condenser, and nitrogen inlet, was charged with 1.61 g (0.005 mole) of crude bromo ketal LII (R=Br), 1.9053 g (0.025 mole) of lithium carbonate, 1.7343 g (0.02 mole) of anhydrous lithium bromide, and 50 mL of dry DMF. The flask was heated at 140°C for 1 h. After cooling the solids were removed by filtration. The residue was taken up in ether and washed with water. After drying ($MgSO_4$) the ether was removed *in vacuo* to afford an oil, 0.6339 g (57.1%). The oil could be distilled (bulb to bulb) *in vacuo* to afford 0.3229 g (29.1%) of what appeared from the ^{1}H-NMR to be the desired dienone ketal LI. IR was not taken. NMR(CCl_4); δ 1.3 (br s, 3H), 2.1 (m, 6H), 4.0 (m, 4H), 6.4-7.5 (m, 3H). There were major impurities at 1.0 and 2.5 ppm.

10. Preparation of α-Phenylseleno Ketal LII (R=SePh):

The general procedure of Reich and co-workers[73] or Caine and co-workers[74] was followed. A 100 mL oven dried three necked round bottomed flask equipped with nitrogen inlet, 10 mL dropping funnel, and rubber septum was charged with 1.9843 g (0.0196 mole) of freshly distilled diisopropylamine and 25 mL of dry THF. To the magnetically stirred solution at 0°C was added, by syringe through the septum, 8.4 mL (0.0216 mole) of 2.4 M n-butyllithium. The solution was stirred for 0.5 h at 0°C and then brought to -78°C. The mono ketal LI (2.2541 g, 0.010 mole) in 10 mL of THF was added dropwise over 10 minutes and stirring was continued for 0.5 h at -78°C. Phenylselenenyl chloride (Aldrich) (3.6048 g, 0.0188 mole) in 10 mL of THF was added over 10 minutes and the flask was allowed to raach ambient temperature during 1.5 h. The reaction mixture was poured onto saturated ammonium chloride and extracted with ether (200 mL). The ether layer was washed sequentially with 10% hydrochloric acid, saturated sodium bicarbonate, and brine. After the ether layer was dried ($MgSO_4$) and evaporation in vacuo, the crude selenide LII (R=SePh) was obtained in ca. 70% yield. The remaining material in the mixture was unchanged L. The orange-red selenide LII (R=SePh) was not purified further.

NMR(CCl_4); δ 1.28 (s, 3H), 1.6-2.5 (m, 8H), 3.8 (m, 4H), 4.2 (m, 1H), 5.75 (s, 1H), 7.4 (m, 5H).

11. Preparation of Cross-Conjugated ketal LI From oxidation of Selenide LII (R=SePh);

A 100 mL three necked round bottomed flask equipped with a magnetic stirring bar, dropping funnel, and thermometer was charged with approximately 3.77 g (0.01 mole) of crude selenide LII (R=SePh) and 50 mL of dry ethyl acetate. An explosion screen was placed in front of the apparatus and 3.4973 g (0.0309 mole) of 30% hydrogen peroxide were added dropwise at 0-5°C. The orange-red selenide turned yellow after the addition. The solution was stirred for 0.75 h at ambient temperature. The mixture was filtered and poured onto water. The organic layer was washed with sodium bicarbonate and satd. sodium chloride. The organic layer was dried ($MgSO_4$) and volatiles were removed in vacuo affording 1.5562 g (70.7%) of cross-conjugated ketal LI. This material was approximately 70% pure (from ^{1}H-NMR), the impurity being unchanged ketal L. This material resisted all attempts at purification. Attempted ketal hydrolysis resulted in decomposition of LI.
NMR(CCl_4); δ 1.32 (br s, 3H), 2.6 (m, 6H), 4.0 (m, 4H), 6.7 (m, 3H).

12. Preparation of trans - Keto Ketal LVI:

The procedure of G. Bauduin was followed with some modifications.[69b] A 2 L three necked round bottomed flask fitted with

an all glass mechanical stirrer, dry ice condenser, and dropping funnel was charged with 1 L of liquid ammonia. To the liquid ammonia maintained at -60°C was added 2.1146 g (0.304 mole) of lithium wire in small portions. To the vigorously stirred blue reducing medium was added 10.4859 g (0.047 mole) of ketal L in 75 mL of dry THF. The reaction mixture was stirred for 45 minutes at -60°C, then 50 mL of satd. aqueous ammonium chloride were added and the ammonia was allowed to evaporate overnight. The crude product was taken up in ether (500 mL) and washed with water, then dried (K_2CO_3) and concentrated *in vacuo*. Distillation of the residue afforded 8.6077 g (81.8%) of LVI. bp 132-137°C (0.4 mm), (lit.[69b] mp 34-36°C).
IR(CCl_4); 2990, 2960, 2890, 1710, 1465, 1180, 1050 $cm.^{-1}$
NMR(CCl_4); δ 1.15 (s, 3H), 1.5-2.5 (m, 13H), 3.8 (s, 4H).

13. Preparation of *trans*-Enone Ketal LV:

The procedure was similar to that used in entry 10. *Trans*-ketal LVI (1.0627 g, 0.0047 mole), 0.6474 g (0.0064 mole) of diisopropylamine, 3.2 mL (0.0076 mole) of 2.4 M *n*-butyllithium and 50 mL of dry THF were combined as previously described. The enolate was trapped with 0.9211 g (0.0048 mole) of phenylselenenyl chloride. After the usual work up 1.6940 g (95.1%) of the crude α-phenylseleno ketone was obtained. TLC examination showed at least three spots, but there was no starting material present. The crude selenide was oxidized in the

usual way: Crude selenide (1.6940 g, 0.0045 mole) treated with 1.6547 g (0.0146 mole) of 30% hydrogen peroxide in 25 mL of dichloromethane, with 0.8 mL of pyridine as buffer, afforded 1.2252 g of crude product. TLC indicated the formation of a number of products. ^{1}H-NMR revealed the presence of the desired compound along with a small amount of mono ketal L, and some selenium containing material. The presence of selenium could be inferred from the ^{1}H-NMR absorption at 7.4 ppm indicating some phenylseleno ketone had survived the oxidation procedure. Owing to the non-regiospecific generation of the enolate anion, and the presence of selenium containing products, this approach was abandoned.
NMR(CCl_4) (100 MHz); δ 1.1 (s, 3H), 0.9-2.5 (mixture of H from L and LV), 3.9 (ketal H, mixture of L and LV), 5.67 (d, 1H, J = 10Hz), 6.85 (d, 1H, J = 10Hz), 7.25 (m, 5H, phenyl H from selenium containing material).

14. Preparation of Trans-1-methoxy-3-trimethylsilyloxy-1,3-butadiene LIX:[77]

The procedure of Danishefsky and Kitahara was followed.[77] A 2 L three necked round bottomed flask equipped with a mechanical stirrer, 500 mL dropping funnel, amd reflux condenser with KOH drying tube was charged with 231 g (2.287 mole) of triethylamine and 4.1 g of freshly powdered anhydrous zinc chloride. The mixture was stirred for 1 h or until the Lewis

acid had become suspended in the amine. Trans-4-methoxy-3-buten-2-one LX (101 g, 1.00 mole) (freshly distilled) in 300 mL of benzene was added. To the clear solution was added 218 g (2.007 mole) of chlorotrimethylsilane dropwise. The reaction mixture turned to a beautiful cherry purple and then deep red. After the addition (about 1.5 h) the reaction mixture was heated at 40-50°C overnight. The contents of the flask were then poured onto 2 L of ether and the suspended triethylamine hydrochloride was removed by filtration. Concentration of the ether and distillation of the residue afforded 116 g (67%) of butadiene LIX, 93% pure by GC analysis. bp 44-45°C (1-2 mm), (lit.[77] bp 54-55°C (5 mm)).
IR($CHCl_3$); 3030, 2985, 2950, 2855, 1680(starting LX), 1656, 1618, 1597, 1565, 1300, 1230, 1010, 950 $cm.^{-1}$
NMR(CCl_4); δ 0.23 (s, 9H), 3.57 (s, 3H), 4.05-4.20 (br s, 2H), 5.36 (d, 1H, J = 12 Hz), 6.81 (d, 1H, J = 12 Hz).

15. Preparation of 2-Methyl-2-cyclohexenone LXI:[79]

The Organic Syntheses procedure of Warnhoff and co-workers was followed.[79] A 2 L three necked round bottomed flask fitted with an all glass mechanical stirrer, a dropping funnel, and a gas outlet, was charged with 100.38 g (0.8948 mole) of 2-methylcyclohexanone LXII in 500 mL of dry carbon tetrachloride. Sulfuryl chloride (133 g, 0.99 mole) in 150 mL of dry carbon tetrachloride was added to the rapidly stirred

solution over a 1 h period. The slightly exothermic reaction was moderated with a cold water bath. Stirring was continued for 2 h after the addition. The solution was then washed successively with 3x150 mL of water, 2x100 mL of satd. aqueous sodium bicarbonate, and 200 mL of brine. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The crude chlorocyclohexanone was added to a 1 L three necked flask fitted with a mechanical stirrer and two reflux condensers. Collidine (121.71 g, 1.00 mole) was added and the flask was heated to 145-150°C. A rapid reaction occurred and benzene was added slowly as the reaction cooled. Solids were collected and washed with 2x300 mL of benzene. The benzene layer was washed with 2x200 mL of 10% hydrochloric acid, 200 mL of satd. aqueous sodium chloride, 200 mL of satd. aqueous sodium bicarbonate, and 200 mL of brine. The benzene layer was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled through a Vigreux column to afford 53.2929 g (54.1%) of enone LXI. bp 70-75°C (22 mm), (lit.[79] bp 98-101°C (77 mm)). IR(neat); 2960, 2940, 1670, 1430, 1360 $cm.^{-1}$
NMR(CCl_4); δ 1.70 (br s, 3H), 1.9-2.5 (m, 6H), 6.65 (m, 1H).

16. Preparation of Cis-Δ^1-3,8-octalindione XXXVII.[78a,b]

The procedure of Danishefsky and Kitahara was followed with some modifications.[78a,b] In a typical large scale experiment five heavy walled glass tubes were filled with a total

of 24.1318 g (0.2194 mole) of enone LXI, 126.62 g (0.7358 mole, 3.35 equivalents) of butadiene LIX, and 1.00 g of hydroquinone. The tubes were blanketed with nitrogen and then the contents of the tubes were solidified using liquid nitrogen. The tubes were evacuated, blanketed with nitrogen, and evacuated again before they were sealed *in vacuo*. The five tubes were heated at 200°C for 48 h. After cooling, the entire contents of the tubes were poured onto a rapidly mechanically stirred mixture of ether (700 mL) and 10% hydrochloric acid (500 mL) maintained at 0-5°C. The stirring was continued for 1 h. The layers were separated and the aqueous phase was extracted with 400 mL of ether. The combined ether extracts were then washed successively with cold 10% sodium hydroxide (4x500 mL) until the dark color had been removed, then with 2x300 mL of brine. The ether was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on silica gel and eluted with 10-20% ether in petroleum ether. Unchanged enone LXI (2.37 g) was recovered in the first fractions. Continued elution afforded octalone XXXVII (13.51 g, 38.4% based on recovered starting material). mp(ether/petroleum ether) 53-55°C, (lit.[78a] 54-55°C).

In smaller scale experiments the yield could be improved to 45%. IR($CHCl_3$); 3025, 2955, 2890, 1710, 1680, 1620, 1460, 1430 $cm.^{-1}$ NMR(CCl_4); δ 1.43 (s, 3H), 1.8-2.6 (m, 9H), 5.96 (d, 1H, J = 10 Hz), 6.66 (d, 1H, J = 10 Hz).

17. Preparation of Triketo Ester LXV:

In a typical experiment a 100 mL three necked round bottomed flask equipped with a magnetic stirring bar, reflux condenser, nitrogen inlet, and drying tube, was charged with 3.6247 g (0.0204 mole) of octalindione XXXVII, 4.6705 g (0.0356 mole) of tert-butyl acetoacetate LVIII, 0.4782 g (0.0042 mole) of solid potassium tert-butoxide, and 70 mL of dry t-butyl alcohol. The reactants were refluxed for 24 h, then additional ester LVIII and butoxide (approximately 100 mg each) were added and reflux was continued another 24 h. After this time TLC showed starting material had been completely consumed. The reaction mixture was poured onto chloroform or ethyl acetate and washed with water. After drying the organic layer over sodium sulfate and evaporation of volatiles, the crude ester was obtained in high yield, ca. 90% as an oil. This material could be used as is in the subsequent step, or the ester LXV could be crystallized from ether or ethyl acetate. Trituration of the oily ester LXV with ether resulted in the crystallization of 4.4127 g (64.5%) of pure triketo ester LXV. mp(EtOAc) 243-253°C

IR(CCl_4); 2950, 1730, 1700, 1630, 1530 $cm.^{-1}$

NMR($CDCl_3$); δ 1.47 (s, 9H), 1.3-3.5 (m, 19H).

18. Synthesis of 13-Methyl-3,4,5,6,7,8,9,10,11,12,13-undecahydro-3,7-phenalenedione LXIII:[80]

Into each of six separate 100 mL three necked round bottomed flasks equipped with a magnetic stirring bar, nitrogen inlet, reflux condenser, and calcium chloride drying tube, was placed a total of 11.78 g (0.035 mole) of crystalline triketo ester LXV (equally divided in the six flasks). p-Toluenesulfonic acid (100 mg) and 70 mL of glacial acetic acid were placed in each flask and the contents were heated at 80-90°C for 3.5 h. After cooling, the reaction contents were poured onto dilute sodium hydroxide and extracted into ethyl acetate. The ethyl acetate was washed with brine, dried ($MgSO_4$), and concentrated in vacuo to yield an oil. TLC indicated the oil was composed of two components. The oil was chromatographed on silica gel and eluted with 30% ether/petroleum ether affording crystalline LXIII (3.192 g, 41.8%). An analytical sample was prepared by two sublimations at 75-80°C (1 mm), mp 84-85°C. Note, acetic acid could be replaced with trifluoroacetic acid with essentially identical results.

IR(CCl_4); 2920, 1720, 1675, 1620, 1550, 1430, 1250 $cm.^{-1}$

NMR(CCl_4); δ 1.23 (s, 3H), 1.5-3.0 (m, 14H), 5.79 (s, 1H).

MS(70 eV); 218 (M^+), 190, 176, 161, 148, 135 (base), 134, 133, 122, 121, 106, 105.

Analysis: Calculated for $C_{14}H_{18}O_2$; C, 77.06, H, 8.25

Found; C, 77.28, H, 8.30

Further elution of the column afforded tricyclic alcohol LXVI (1.82 g, 22%), mp(EtOAc) 125-126°C.
IR(KBr); 3500, 2990, 1710, 1700, 1490, 1470, 1300, 1230, 1080, 1070, 1055 $cm.^{-1}$
NMR(CCl_4); δ 1.23 (s, 3H), 1.7-3.2 (m, 16H), 4.22 (s, 1H, exchanges with D_2O).
MS(70 eV); 236 (M^+), 221, 218, 179, 175, 161, 151, 147, 135, 134, 133, 132, 126, 124, 123, 122, 121, 119, 111 (base), 110, 109, 108, 107, 105.

19. Preparation of Hydroxy Enone LXXI:

To 0.5115 g (0.0023 mole) of enedione LXIII and 50 mL of 95% ethanol in a 125 mL flask equipped with a magnetic stirring bar, was added 0.0583 g (0.0015 mole) of sodium borohydride in small portions during 15 minutes at 0-5°C. The reaction contents were kept at this temperature for 15 minutes, and then stirred at ambient temperature for 30 minutes. After addition of 10 mL of 10% acetic acid, the flask was heated on a steam bath for 20 minutes. The reaction contents were extracted into ethyl acetate and washed with satd. aqueous sodium bicarbonate and brine. After drying the organic layer with magnesium sulfate and concentration *in vacuo*, a quantitative yield (0.51 g) of hydroxy enone LXXI was obtained. TLC indicated a mixture of isomers. This material was used without further purification.

IR($CHCl_3$); 3400, 3020, 2980, 1680, 1640, 1450, 1250, 1050, 1020 $cm.^{-1}$

NMR(CCl_4); δ 1.2 (m, 3H), 1.4-2.7 (m, 14H), 3.5-4.0 (m, 2H), 5.7 (s, 1H).

20. Preparation of Dienone LXXII:

Approximately 0.51 g (0.0023 mole) of crude hydroxy enone LXXI and freshly pulverized anhydrous potassium bisulfate were heated at 155°C (0.25 mm) until a yellow liquid distilled. A heat gun was used to expedite the distillation at this point, which afforded 0.4032 g (92.7%) of dienone LXXII.

IR(CCl_4); 3010, 2980, 1700, 1650, 1630, 1470, 1450, 1250 $cm.^{-1}$

NMR(CCl_4); δ 1.08 (s, 3H), 1.7-2.4 (m, 12H), 5.8 (m, 3H).

This compound could also be prepared by mesylation of LXXI and dehydromesylation using DBN or DBU.[89] Overall yields were lower using this two step procedure.

21. Preparation of tricyclic Enediol LXX:

A 300 mL three necked round bottomed flask fitted with a reflux condenser, nitrogen inlet, drying tube, 50 mL dropping funnel, and magnetic stirring bar, was charged with 100 mL of anhydrous ether and 0.2717 g (0.0072 mole) of lithium aluminum hydride. To this rapidly stirred suspension, maintained at 0-5°C, was added over 0.5 h 1.001 g (0.0045 mole) of enedione LXIII in 30 mL of dry ether and 10 mL of dry THF. The

reaction mixture was allowed to return to ambient temperature and stirred for 16 h. The flask was then cooled to 0-5°C and water (5 mL) was carefully added. The reaction contents were continuously extracted using ether or ethyl acetate. The organic extract was dried ($MgSO_4$) and concentrated *in vacuo* to afford the desired diol, 0.7623 g (74.9%). The diol LXX was used without further purification.

IR(CCl_4); 3300-3500, 2990, 2950, 1640, 1440, 1300, 1030 $cm.^{-1}$

NMR(CCl_4); δ 1.22 (m, 3H), 1.0-2.2 (m, 14H), 3.7 (m, 2H), 5.4 (m, 2H exchanges with D_2O), 6.1 (s, 1H).

22. Synthesis of 13-Methyl-5,8,9,10,11,12,13-heptahydrophenalene LXVII:[83]

Enediol LXX (0.7623 g, 0.0034 mole) and freshly pulverized potassium bisulfate (4.65 g, 0.034 mole) were combined and distilled at 150-170°C (0.25 mm) to afford 0.3917 g (61.3%) of a two component mixture (TLC). The mixture was separated by preparative layer chromatography (elution with petroleum ether) to afford 0.2437 g (38.2%) of tricyclic triene LXVII and 0.0651 g of dienol LXXIV. Dienol LXXIV could be converted to triene LXVII by treatment with potassium bisulfate. Gas chromatographic analysis showed that triene LXVII was very slightly contaminated with three other components.

UV(cyclohexane); 239 nm (ε = 14080).

IR(CCl_4); 3050, 2950, 2920, 1650, 1600, 1550, 1450 $cm.^{-1}$

^{1}H-NMR($CDCl_3$); δ 0.98 (s, 3H), 1.5-2.2 (m, 10H), 5.3-6.3 (m, 5H).
^{13}C-NMR($CDCl_3$); δ 20.580 (CH_3), 26.237, 29.017, 29.529, 31.212, 33.186, 35.747 (C_{13}), 44.403 (C_5?), 123.702, 124.139 (Two C-atoms for this signal), 129.625, 130.478, 143.577 (C_1).
MS(70 eV); 186 (M^+), 171, 145, 143, 129 (base), 128, 118, 117, 115, 91, 77.

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